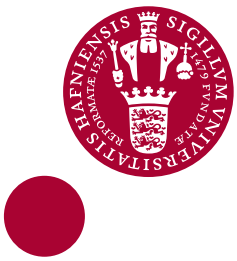

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A Randomized Controlled Trial

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Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke

A Randomized Controlled Trial

Philip M. Bath, DSc, FMedSci; Polly Scutt, MSc; Jo Love, BSc; Pere Clavé, MD, PhD; David Cohen, FRCP; Rainer Dziewas, MD, PhD; Helle K. Iversen, MD, DMSci; Christian Ledl, MA; Suzanne Ragab, FRCP, MPhil; Hassan Soda, MD, PhD; Anushka Warusevitane, MRCP(UK); Virginie Woisard, MD, PhD; Shaheen Hamdy, FRCP, PhD; on behalf of the Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPS) Trial Investigators

Background and Purpose—Dysphagia is common after stroke, associated with increased death and dependency, and treatment options are limited. Pharyngeal electric stimulation (PES) is a novel treatment for poststroke dysphagia that has shown promise in 3 pilot randomized controlled trials.

Methods—We randomly assigned 162 patients with a recent ischemic or hemorrhagic stroke and dysphagia, defined as a penetration aspiration score (PAS) of ≥3 on video fluoroscopy, to PES or sham treatment given on 3 consecutive days. The primary outcome was swallowing safety, assessed using the PAS, at 2 weeks. Secondary outcomes included dysphagia severity, function, quality of life, and serious adverse events at 6 and 12 weeks.

Results—In randomized patients, the mean age was 74 years, male 58%, ischemic stroke 89%, and PAS 4.8. The mean treatment current was 14.8 (7.9) mA and duration 9.9 (1.2) minutes per session. On the basis of previous data, 45 patients (58.4%) randomized to PES seemed to receive suboptimal stimulation. The PAS at 2 weeks, adjusted for baseline, did not differ between the randomized groups: PES 3.7 (2.0) versus sham 3.6 (1.9), P=0.60. Similarly, the secondary outcomes did not differ, including clinical swallowing and functional outcome. No serious adverse device-related events occurred.

Conclusions—In patients with subacute stroke and dysphagia, PES was safe but did not improve dysphagia. Undertreatment of patients receiving PES may have contributed to the neutral result.

Clinical Trial Registration—URL: http://www.controlled-trials.com. Unique identifier: ISRCTN25681641.

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Key Words: dysphagia ■ pharyngeal electrical stimulation ■ randomized controlled trial ■ stroke

Acute stroke is complicated by oropharyngeal dysphagia in 50% of patients; of these, up to 40% remain dysphagic a year later.[1] Dysphagia is complicated by aspiration, pneumonia, and malnutrition,[2] and patients need enteral feeding through a nasogastric tube or percutaneous endoscopically introduced gastrostomy tube, which often requires long-term institutional care.[3] Although dysphagia may be treated using several physical and behavioral techniques, there are no definitive treatments.[4]

Human swallowing has bilateral representation in the cerebral hemispheres with a dominant cortex (unrelated to handedness).[5] Dysphagia often follows a stroke that affects the dominant swallowing cortex, which is then exacerbated in recurrent strokes. Swallowing is dependent on afferent feedback via bulbar cranial nerves innervating the pharynx, and increased sensory input from the pharynx can drive long-term beneficial changes in the cortical control of

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From the Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, United Kingdom (P.M.B., P.S.); Phagenesis, Ltd, Manchester Science Park, United Kingdom (J.L.); Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Hospital de Mataró, Universitat Autònoma de Mataró, Spain (P.C.); Stroke Service, Northwick Park Hospital, London, United Kingdom (D.C.); Department of Neurology, University Hospital Münster, Germany (R.D.); Department of Neurology, Glostrup Hospital and University of Copenhagen, Denmark (H.K.I.); Schoen Klinik Bad Aibling, Bad Aibling, Germany (C.L.); Stroke Service, Poole Hospital, Poole, United Kingdom (S.R.); Neurology Clinic, Bad Neustadt, Germany (H.S.); Acute Stroke Unit, University Hospitals of North Midlands, Stoke-on-Trent, United Kingdom (A.W.); Unité de la voix et de la deglutition, Service ORL CHU de Toulouse, Octogone Lordat Université Toulouse Mirail, France (V.W.); and Centre for Gastrointestinal Sciences, University of Manchester, United Kingdom (S.H.).

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Correspondence to Philip M. Bath, DSc, FMedSci, Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, United Kingdom. E-mail philip.bath@nottingham.ac.uk

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swallowing[6] with functionally relevant reorganization of the swallowing cortex.[6,7]

During development of pharyngeal electric stimulation (PES), a study in healthy volunteers[8,9] suggested that PES should be delivered at 5 Hz for 10 minutes with an electric current of threshold plus 75% of the difference between threshold and tolerance levels, a paradigm that produced the largest effect on brain excitability.[8,10] Using this approach in patients with subacute stroke in a randomized dose-comparison trial, PES reduced radiological aspiration, manifest as a reduction in penetration aspiration score (PAS).[9] Similarly, PES reduced clinical dysphagia (assessed using the dysphagia severity rating scale [DSRS]) and length of stay in hospital in patients with dysphagia post stroke in a sham-controlled parallel-group phase II trial.[9] In a further multicentre phase II randomized sham-controlled trial, PES was associated with nonsignificant tendencies to reduced clinical dysphagia and shorter length of stay in hospital.[11] An individual patient data meta-analysis of these 3 trials found that PES significantly reduced aspiration (PAS) and dysphagia (DSRS) and was safe and well tolerated.[12] Here, we present the results of a large, randomized, sham-controlled phase III trial of PES in patients with subacute poststroke dysphagia.

Materials and Methods

Participants

We did an international, multicenter, randomized, sham-controlled, patient-masked, outcome assessor–masked, parallel-group trial, as detailed in the online-only Data Supplement. In brief, patients with a recent stroke and videofluoroscopy (VFS)-confirmed dysphagia were randomized to 3 days of PES or sham stimulation, and the primary outcome was the penetration aspiration scale, assessed using VFS, at 2 weeks after the third treatment session.

Patients were eligible for the trial if they were admitted to hospital with a clinical stroke syndrome because of ischemic or hemorrhagic stroke, were aged ≥18 years, had clinical dysphagia identified using bedside testing (as assessed by a nurse or speech and language therapist using a local clinical assessment and confirmed by failure on the Toronto Bedside Swallowing Screening Test), were alert or rousable (score of 0 or 1 on question 1a of the National Institutes of Health Stroke Scale [NIHSS]), had a PAS ≥3 (see the online-only Data Supplement for description) of for at least 1 swallow (assessed using VFS),[13] and could be treated within 42 days of stroke onset. The diagnosis of ischemic or hemorrhagic stroke was confirmed with computed tomography or magnetic resonance imaging performed between hospitalization and enrollment and using standard imaging techniques. Key exclusion criteria included a history of dysphagia, dysphagia from a condition other than stroke, advanced dementia, implanted pacemaker or cardiac defibrillator in situ, unstable cardiopulmonary status or a condition that compromised cardiac or respiratory status, distorted oropharyngeal anatomy, additional diagnosis of a progressive neurological disorder, receiving continuous oxygen treatment, or pregnant or nursing mother.

Ethics and Approvals

The study was approved by national ethics committees and competent authorities in each participating country, and locally at each site, and was adopted by the UK National Institute for Health Research Stroke Research Network. We obtained written informed consent from each patient, or proxy consent from a relative when the patient did not have capacity (eg, because of dysphasia and confusion), before enrollment and in accordance with national regulations; in Germany, the Bundesamt für Strahlenschutz regulatory authority did not allow proxy consent. The trial was run by a Trial Management Committee (P.M.B., S.H., C.M., and J.L.). An independent data-monitoring committee reviewed unmasked data every 6 months. The trial was registered as ISRCTN25681641.

Randomization

VFS (see below) was performed as a study procedure after consent to confirm the presence of dysphagia (PAS ≥3).[14] Investigators entered baseline and follow-up data into a commercial database (Rave, Medidata Solutions, Inc) linked to a randomization list (Quantics Consulting, Ltd). The data were checked to confirm the patient's eligibility, and the system then assigned a participant to treatment with active PES or sham PES with allocation 1:1. Allocation was by randomly permuted blocks (of size 6) with stratification by center and feeding status (presence/absence of artificial feeding) to enhance balance between treatment groups.

VFS

VFS was performed using local protocols at each participating site by a speech and language therapist or a radiologist. At each time point (baseline and weeks 2 and 12), each participant was given up to 6×5 mL bolus drinks of contrast agent (Omnipaque 300 in UK, Visipaque 270 in France, or Accupaque 300) of liquid consistency (≈40% wt/vol). A 50 mL drink of contrast agent was then administered and swallows recorded.

At baseline, bolus drinks were taken until 3 were positive (ie, at least 1 swallow within a bolus of PAS ≥3); once achieved, further bolus drinks were not given to reduce the risk of aspiration and pneumonia. Hence, between 3 and 7 boli (each inducing ≥1 swallows) were administered. Once completed, quality-assured digital VFS image files for each swallow for each bolus were sent immediately to 1 of 2 independent adjudicators who were blinded to clinical information and who confirmed whether the patient fulfilled the inclusion criteria on the basis of aspiration of radiological contrast. Use of digital VFS reduced the risk of image degradation on file transfer. Once confirmation was received, treatment could be started. VFS images at weeks 2 and 12 were similarly uploaded and assessed by 1 of 2 adjudicators who were blinded to patient details and randomization. Silent aspiration was defined as aspiration without an attempted cough as seen on the video file, accompanying sound, or event monitor.

Procedures

Sterile single-patient use treatment catheters (Phagenyx, Phagenesis, Ltd, Manchester, UK), which contain an inner lumen for feeding, were inserted via the nose by trained staff. The catheter was inserted to an aboral depth related to the patient's height so that the pair of ring treatment electrodes located on the outer surface of the catheter were adjacent to the pharynx.

Treatment was started once dysphagia was confirmed by VFS and given daily for 3 days.[9] At each session, the catheter was connected to the controlling base station, and electric current at 5 Hz was increased incrementally from 1 mA to detect threshold (patient first aware of stimulation) and then tolerated (patient does not want current increased further) intensity levels in all patients. Those randomized to active PES were then administered this for 10 minutes at a treatment current (mA) of threshold plus 75% of the difference between threshold and tolerance levels; this paradigm was used successfully in earlier studies of PES and considered to be an effective level of stimulation without being too near the tolerance level.[12] Patients randomized to sham therapy had no stimulation after establishment of threshold and tolerated levels. Patients, but not the treating researcher, were masked to treatment assignment. Treatment could be stopped if the patient withdrew consent, for safety reasons, or if unacceptable adverse events developed.

Active or sham PES treatment was given in addition to standard stroke care, including thrombolysis if administered at admission to hospital, and rehabilitation. Systematic use of antihypertensive agents (all patients), oral antithrombotic and lipid-lowering agents, and carotid endarterectomy (patients with ischemic stroke) were

recommended for secondary prevention as per each site's local practice. The final diagnosis was confirmed at discharge based on clinical presentation and neuroimaging.

Outcomes

The primary outcome measure was radiological aspiration at 2 weeks assessed as the PAS using VFS.[14] The timing of VFS at 2 weeks reflected that used in 3 pilot trials.[12] As a secondary outcome, PAS was also measured at 12 weeks.

Other prespecified secondary outcomes at 2, 6, and 12 weeks included clinical dysphagia (DSRS[9]; see the online-only Data Supplement), dependency (modified Rankin Scale [mRS][15,16]), activities of daily living/disability (Barthel Index[17]), impairment (NIHSS[18]), health-related quality of life (European Quality of Life-5 Dimensions [EQ-5D],[19] from which health utility status was calculated [EQ-5D-HUS]), and nutritional measures (weight, mid-arm circumference, and blood albumin). At discharge from initial admittance to hospital, investigators recorded duration of stay and discharge destination (to institution or home).

The safety outcomes were all-cause case fatality and cause-specific case fatality; serious adverse events and serious adverse device-related events; and cases of chest infection or pneumonia (diagnosed locally because the diagnosis of chest infection and pneumonia is poorly defined[20]).

A member of the central research team (S.H.), who was masked to treatment assignment, validated and categorized investigator-reported serious adverse events, including cause-specific deaths. Patients who did not receive their assigned treatment or who did not adhere to the protocol were followed up in full. The recruiting site, using a separate nontreating researcher who was masked to treatment allocation, did post-treatment follow-ups at 2, 6, and 12 weeks.

Statistical Analyses

The statistical analysis plan was published on the Phagenesis, Ltd, website before data lock and unblinding: http://www.phagenesis.com/wp-content/uploads/2012/09/Statistical-Analysis-Plan-STEPS.pdf (March 21, 2012). The trial was designed to recruit 140 patients so as to detect an absolute reduction in the change in PAS (mean of all swallows from all available boli) from baseline to 2 weeks of 1.1 point (SD 1.8) between the treatment groups, with power 90%, 2-sided significance 5%, and allowance for incomplete data/losses to follow-up in 15% of patients. After analysis of individual patient data from 3 pilot studies,[12] the primary analysis was changed to comparison between the treatment groups of the mean of the worst swallow in each of the 3 to 7 available boli (with adjustment for the same at baseline, and no imputation of missing data) because this seemed to be more robust statistically and was felt to be clinically more relevant, a decision that was made before unblinding of data.

Four analysis populations were created: randomized, all those who were assigned to PES or sham treatment; safety, all randomized patients who had treatment attempted, that is, insertion of the treatment catheter with or without PES/sham; efficacy, all randomized patients who received at least 1 episode of PES/sham treatment and who had the primary outcome (PAS) measured at both baseline and 2 weeks; and per protocol, randomized patients who received all 3 treatments and who had PAS data measured at baseline and 2 weeks.

Swallowing was analyzed as a comparison between the treatment groups using multiple linear regression with adjustment of the on-treatment PAS for baseline PAS, stratification variables (site and feeding status), and prognostic baseline variables (age, sex, and NIHSS). Secondary analyses used multiple linear regression (continuous data, eg, EQ-5D), ordinal logistic regression (ordered categorical data, eg, mRS), binary logistic regression (dichotomous data, eg, PAS ≤3, serious adverse events, and chest infection), and Kaplan–Meier and Cox regression models (time to event, eg, death). 95% confidence intervals (CI) are presented, and $P<0.05$ was considered statistically significant. Analyses were performed using SAS version 9.3. Summary meta-analyses based on group data from Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPS) and earlier trials[9,11] were produced using the Cochrane Collaboration's Review Manager software (version 5.3).

Additional Information

Further information on Materials and Methods is given in the online-only Data Supplement.

Results

Between April 2012 and September 2014, we consented 195 patients; screened 181 patients with VFS; assigned treatment in 162 patients (randomized population); attempted treatment in 152 patients (safety population); treated (with at least 1 session of PES or sham) 141 patients; and obtained VFS in 126 patients at 2 weeks (primary outcome population) and 95 patients at 12 weeks (Figure 1). The reduction in numbers between consent and randomization reflected patients who: screened negative for aspiration on VFS, could not have the catheter inserted, and did not have a VFS 2 weeks after treatment. The 162 randomized patients were recruited from 20 sites in 5 countries (Denmark, France, Germany, Spain, and United Kingdom, listed in the online-only Data Supplement); of these, 87 patients were assigned active PES and 75 patients were assigned to the sham group (Figure 1). Hundred and one patients (62.3%) were recruited from the United Kingdom. The randomized groups were well balanced at baseline (Table 1): mean age 74 (SD 11) years, 94 (58%) were male, and 143 (89%) patients had an ischemic stroke. The mean time from stroke to randomization was 13 (10) days. The Data Monitoring Committee reviewed the trial on 3 occasions and recommended that the trial should continue each time.

Adherence with assignment to active or sham PES was good in 141 participants who received at least 1 treatment session. There were no material differences at baseline in 15 treated participants who did not have VFS at 2 weeks versus 126 treated participants who did have VFS. No patients randomized to sham received active treatment, and all patients with a catheter inserted and randomized to PES received at least 1 active treatment session. The mean treatment stimulation level was 14.5 mA in those randomized to PES, with mean treatment duration 9.8 minutes and mean number of treatments 3.0 (Table I in the online-only Data Supplement). However, evidence of suboptimal treatment current levels seemed to be present: 58% of PES-treated patients had a treatment level <10.2 mA (a figure chosen from earlier research[12]), identical treatment and threshold levels, or a treatment level less than threshold.

In the primary outcome population, the mean PAS at baseline was 4.8 (SD 2.0) and reduced in both active PES and sham PES groups at 2 weeks (Table 2). When adjusted for site, age, NIHSS, baseline feeding status, and PAS, there was no difference in PAS at 2 weeks, mean difference 0.14 (95% CI, −0.37 to 0.64; $P=0.60$; Table 2 and Figure 2); the mean change in PAS from baseline to 2 weeks did not differ between the 2 treatment groups: active PES −1.2 (1.8) versus sham PES −1.2 (1.8) and difference 0.14 (−0.37 to 0.64). Meta-analysis of individual patient data from earlier studies suggested that different approaches to statistical analysis varied in their statistical efficiency;[12] in sensitivity analyses, PAS did not differ between the groups when assessed using different statistical

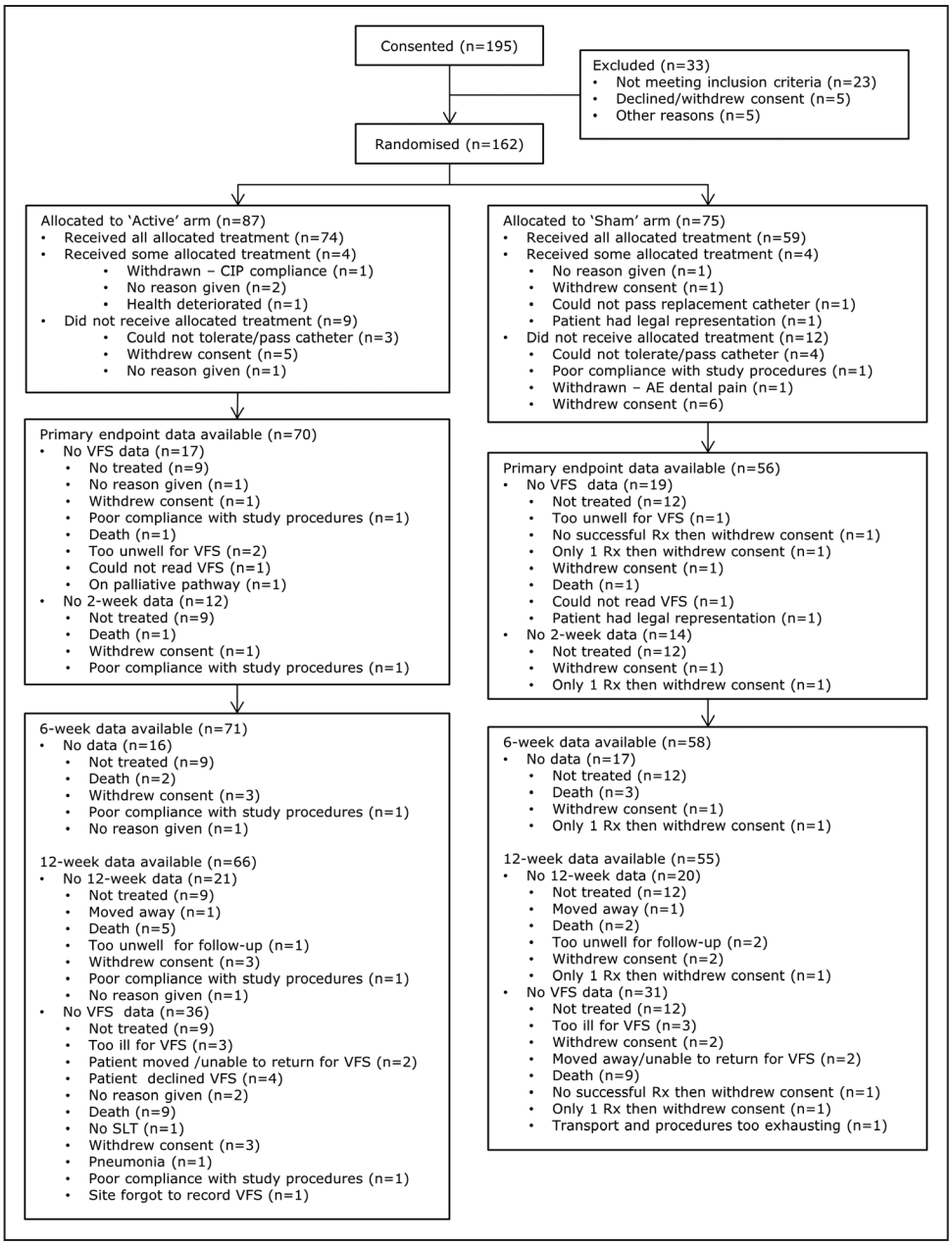

Figure 1. Flow of patients through the trial: consented, 195; screened with VFS, 181; randomized, 162; treatment attempted, 152; treated, 141; treated with VFS at 2 weeks, 126; all 3 treatments received with VFS at 2 weeks, 123; treated with VFS at 12 weeks, 95. AE indicates adverse event; CIP, clinical investigational plan; Rx, randomization; SLT, speech and language therapy; and VFS, videofluoroscopy.

approaches (Table II in the online-only Data Supplement). When assessed in prespecified subgroups, no significant interactions were present (Figure 2).

PES had no significant effects on secondary measures of swallowing and feeding, including radiological aspiration (PAS) at 12 weeks, and clinical dysphagia (DSRS) and feeding route at weeks 2 and 12 (Table 3; Table II in the online-only Data Supplement). Apparent tendencies in favor of PES were present at week 2 (but not at week 12) for functional measures of outcome (mRS and Barthel Index). Other measures did not differ between the treatment groups (Table 3; Table II in the online-only Data Supplement). When assessed in prespecified subgroups, significant interactions were present between clinical dysphagia (DSRS) and treatment assignment for age and PAS (Figure I in the online-only Data Supplement). The number of patients with chest infection or pneumonia occurring after randomization (and so possibly related to VFS rather than subsequent PES/sham treatment) did not differ between the treatment groups: PES 21, sham 11 (P=0.19). The overall rate of serious adverse events occurring by end of follow-up did not differ between the 2 groups, and no serious adverse device-related events occurred in either group (Table III in the online-only Data Supplement). The cumulative risk of all-cause death during follow-up did not differ between the group given PES and the sham treatment (Figure II in the online-only Data Supplement). The

Table 1. Baseline Characteristics in the Randomized Population by Treatment Assignment

	N	Randomized	PES	Sham
Patients	162	162	87	75
Age, y	162	74.4 (11.2)	74.0 (9.9)	74.9 (12.6)
Sex, male (%)	162	94 (58.0)	48 (55.2)	46 (61.3)
Race/ethnicity (%)	162			
Asian		15 (9.3)	9 (10.3)	6 (8.0)
Black		4 (2.5)	0 (0.0)	4 (5.3)
White		139 (85.8)	74 (85.1)	65 (86.7)
Other		4 (2.5)	4 (4.6)	…
Modified Rankin Scale (/6)	153	4.0 (1.1)	3.9 (1.1)	4.1 (1.2)
Barthel Index (/100)	153	28.4 (29.8)	32.4 (31.7)	23.8 (26.8)
Stroke, previous (%)	162	23 (14.2)	15 (17.2)	8 (10.7)
Visible on imaging (%)	161	42 (26.1)	25 (28.7)	17 (23.0)
Stroke type (%)	161			
Ischemic/normal		143 (88.8)	77 (89.5)	66 (88.0)
Intracerebral hemorrhage		17 (10.6)	9 (10.5)	8 (10.7)
Nonstroke		1 (0.6)	0 (0)	1 (1.3)
Side of CT lesion (%)	158			
Left		63 (39.9)	33 (38.4)	30 (41.7)
Right		69 (43.7)	36 (41.9)	33 (45.8)
No lesion		26 (16.5)	17 (19.8)	9 (12.5)
Syndrome (%)	157			
Total anterior circulation		41 (26.1)	21 (24.4)	20 (28.2)
Partial anterior circulation		69 (43.9)	44 (51.2)	25 (35.2)
Lacunar		46 (29.3)	21 (24.4)	25 (35.2)
Posterior circulation		1 (0.6)	0 (0.0)	1 (1.4)
Severity, NIHSS (/42)	152	9.9 (6.4)	9.6 (6.5)	10.2 (6.2)
Dysphasia, NIHSS (%)	152	55 (36.2)	29 (35.8)	26 (36.6)
Onset to randomization (days)	162			
Mean (SD)		13.4 (9.7)	12.6 (9.5)	14.4 (10.0)
Median (IQR)		11 (6–18)	10 (5–17)	12 (6–21)
DSRS (/12)	154	7.6 (3.8)	8.0 (3.9)	7.0 (3.5)
TOR-BSST, failed (%)	162	158 (97.5)	85 (97.7)	73 (97.3)
Feeding route (%)	162			
Oral, normal diet		10 (6.2)	5 (5.7)	5 (6.7)
Oral, soft diet		45 (27.8)	23 (26.4)	22 (29.3)
Nasogastric		90 (55.6)	52 (59.8)	38 (50.7)
PEG		4 (2.5)	3 (3.4)	1 (1.3)
Other		13 (8.0)	4 (4.6)	9 (12.0)
Weight (kg)	153	71.9 (16.4)	71.9 (15.3)	72.0 (17.6)
Body mass index (kg/m^2)	148	25.2 (5.0)	25.7 (4.8)	24.7 (5.2)
Mid-arm circumference (cm)	143	28.3 (3.6)	28.2 (3.7)	28.5 (3.6)
Albumin (g/L)	144	36 (5.7)	36.4 (5.8)	35.5 (5.6)
Chest infection (%)	156	8 (5.1)	3 (3.6)	5 (6.9)
Penetration aspiration scale (/8)	162	4.7 (2.0)	4.7 (2.1)	4.7 (1.9)
PAS >2	162	148 (91.4)	79 (90.8)	69 (92.0)

Data are number (%), median (interquartile range), or mean (SD). CT indicates computed tomography; DSRS, dysphagia severity rating scale; NIHSS, National Institutes of Health Stroke Scale; PAS, penetration aspiration score; PEG, percutaneous endoscopic gastrostomy; and TOR-BSST, Toronto Bedside Swallowing Screening Test.

Table 2. PAS at 2 Weeks in the Efficacy Population by Treatment Assignment

	All (N=126)	PES (N=70)	Sham (N=56)	OR/MD (95% CI), Adjusted	*P* Value	OR/MD (95% CI), Unadjusted	*P* Value
Baseline							
PAS (/8)	4.8 (2.0)	4.8 (2.1)	4.7 (1.9)	…	…	…	…
2 wk primary outcome							
Mean of all boli (/8)	3.6 (2.0)	3.7 (2.0)	3.6 (1.9)	0.14 (–0.37 to 0.64)	0.60	0.06 (–0.62 to 0.74)	0.86
Change from baseline	–1.2 (1.8)	–1.2 (1.8)	–1.2 (1.8)	0.14 (–0.37 to 0.64)	0.60	0.00 (–0.62 to 0.61)	1.00
Any PAS >3 (%)	105 (83.3)	60 (85.7)	45 (80.4)	1.22 (0.29 to 5.15)	0.79	1.47 (0.57 to 3.75)	0.42
12 wk							
Mean of all boli (/8)	3.2 (2.1)	3.3 (2.2)	3.0 (2.1)	0.29 (–0.04 to 0.99)	0.41	0.24 (–0.6 to 1.08)	0.57
Any PAS >3 (%)	69 (72.6)	36 (70.6)	33 (75.0)	0.62 (0.20 to 1.90)	0.41	0.80 (0.32 to 1.99)	0.63
Repeated measures							
Mean (/8)*	…	4.1 (2.3)	3.9 (2.3)	0.51 (–0.23 to 1.25)	0.18	0.19 (–0.67 to 1.04)	0.67

All patients had diagnostic videofluoroscopy at both baseline and 2 weeks and received at least 1 treatment session. Data are number (%), median (interquartile range), or mean (SD), with comparisons using unadjusted and adjusted multiple linear, ordinal logistic, or binary logistic regression. CI indicates confidence interval; MD, mean difference; OR, odds ratio; PAS, penetration aspiration score; and PES, pharyngeal electric stimulation.

*Includes death: PAS=9.

treatment equipment was rated as easy to use by investigators who operated the PES treating device; however, passing the catheter was rated as difficult in one third of investigators (Table IV in the online-only Data Supplement).

In a summary meta-analysis of results from STEPS and earlier trials,[9,11] there was no difference in PAS between patients randomized to PES versus sham (Figure III in the online-only Data Supplement). In contrast, PES was associated with a larger reduction (ie, improvement) in DSRS than patients randomized to sham, mean difference –0.94 (95% CI, –1.85 to –0.03; *P*=0.04; Figure IV in the online-only Data Supplement).

Discussion

In patients with dysphagia post stroke, PES had no significant effect on radiological aspiration or clinical dysphagia, assessed as PAS and dysphagia severity rating scale, respectively. Similarly, PES had no effect on dependency (mRS), disability (Barthel Index), or impairment (NIHSS). No safety issues were identified.

The explanation for these largely neutral results remains unclear but many possibilities need to be examined. First, PES may simply not be effective for treating dysphagia after stroke; however, this seems unlikely in the context of a positive individual patient data meta-analysis of earlier poststroke PES studies,[9,11,12] the positive summary meta-analysis for DSRS presented here, and positive trials in multiple sclerosis and stroke patients with a tracheostomy.[21,22] Second, the severity of dysphagia at baseline will itself determine the likely success of treatment. Across the field of acute stroke, it is challenging to demonstrate efficacy in a group of patients with mild impairment because many patients will regain normal function spontaneously; in this context, mild dysphagia is likely to resolve spontaneously. Importantly, the regulatory authority in 1 country (Germany) limited recruitment to patients who could provide consent for themselves, and this resulted in inclusion of patients with only milder stroke and aspiration, a decision that would challenge demonstrating efficacy for many interventions. Although the mean baseline PAS in STEPS (PAS=4.8) was similar to previous stroke trials of PES (4.3[12]; Table V in the online-only Data Supplement), it was lower than in a positive trial in multiple sclerosis (PAS=6.5[21]). Of relevance, patients randomized to sham in the earlier studies tended to have minimal or no overall improvement in PAS or DSRS, whereas sham patients in STEPS showed improvement (Table V in the online-only Data Supplement). Confounding this point is the potential relevance of VFS to the diagnosis of dysphagia and its severity; in particular, PAS scores were noted to be highly variable during administration of contrast boli. Additionally, VFS was not readily available at many sites thereby limiting recruitment. We chose PAS (using thin boli) as a primary outcome measure based on previous pilot studies which showed a significant improvement in this measure in the active PES arm[8,9] but recognize that PAS alone does not capture information about swallowing efficiency and bolus control as might come from using thick liquid boli and measures of pharyngeal residue/timings.

Third, and related to the issue of severity and spontaneous resolution, patients who are enrolled early after stroke will comprise a mixed group of those with severe dysphagia and those with milder dysphagia that will improve without treatment. However, later recruitment will enhance the proportion of patients with severe (or fixed) dysphagia. In reality, STEPS and earlier trials each recruited patients at ≈2 weeks poststroke.[12] Fourth, participants received variable amounts of active speech and language therapy, and this may have confounded the effect of additive PES.

Fifth, patients randomized to PES may have received subtherapeutic stimulation levels because mean levels were lower in STEPS (mean treatment 14.8 mA) than in previous positive

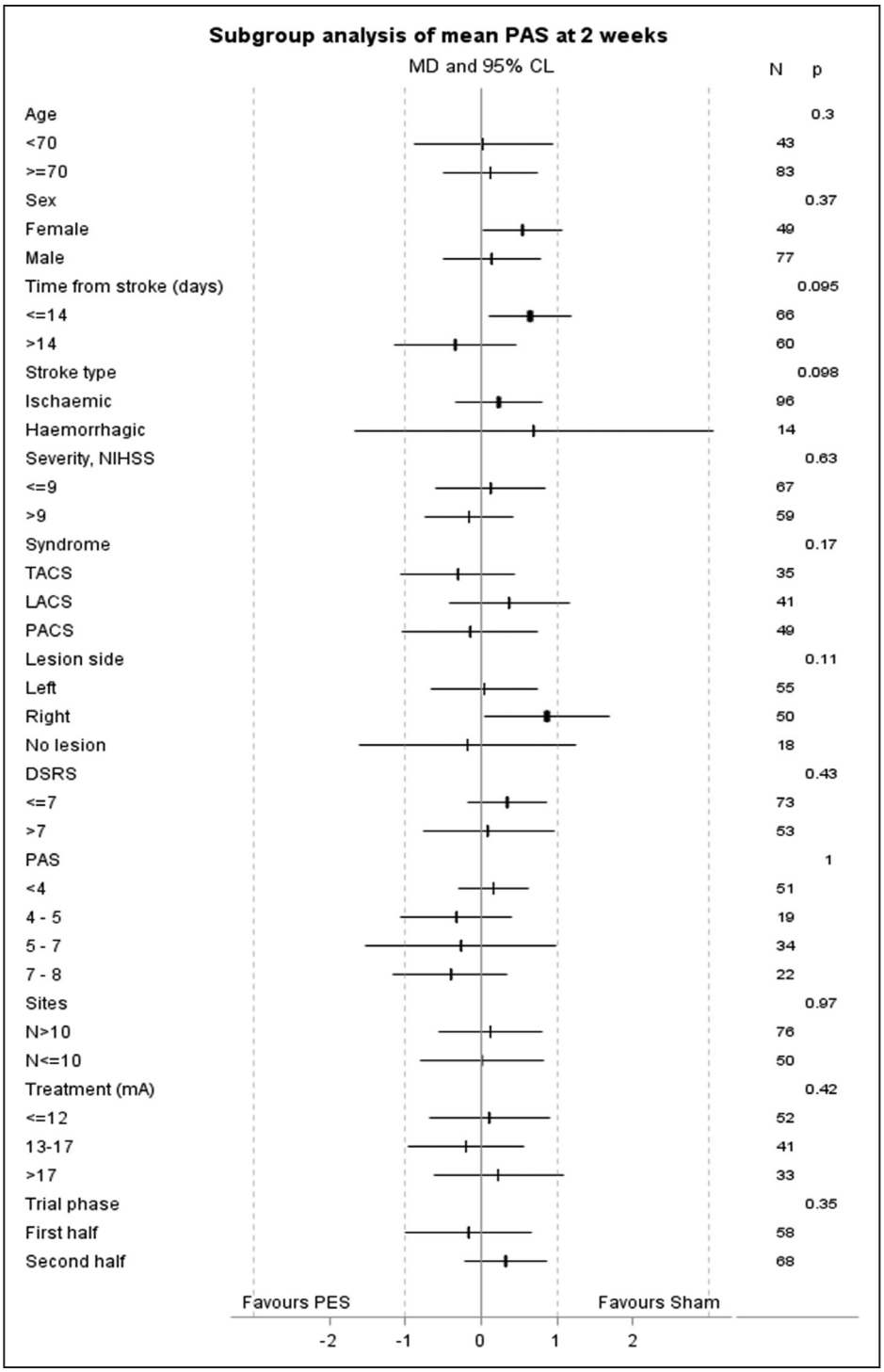

Figure 2. Effect of treatment on penetration aspiration score in prespecified subgroups determined at baseline, with analysis using adjusted multiple linear regression. CL indicates confidence limit; DSRS, dysphagia severity rating scale; LACS, lacunar circulation syndrome; MD, mean difference; NIHSS, National Institutes of Health Stroke Scale; PACS, partial anterior circulation syndrome; PAS, penetration aspiration score; PES, pharyngeal electric stimulation; and TACS, total anterior circulation syndrome.

trials in stroke (16.8 mA[12]). Using a treatment level of <10.2 mA (mean − 1 SD in previous trials[12]) or treatment threshold level ≤0 mA, 58% of participants randomized to PES may have been undertreated. Importantly, the magnitude of stimulation has been shown previously to be associated with improvement in aspiration.[8] Investigator concerns about the potential to harm patients seem to have explained this situation, although the study showed no evidence of harm, and PES may be delivered safely up to 50 mA (the maximum that can be delivered by the base station), as shown in another study in patients with stroke.[22] And last, assessment of threshold and tolerance levels in patients randomized to sham PES may have amounted to an element of stimulation. For example, a participant randomized to sham but who had high threshold and tolerance currents

Table 3. Clinical and Safety Outcomes by Treatment Assignment in Patients Who Received At Least 1 Active or Sham Treatment and Who Had Outcome Measured

	N	All	PES	Sham	OR/HR/MD	*P* Value Adjusted	OR/HR/MD	*P* Value Adjusted
2 wk								
DSRS (/12)*	133	5.1 (3.8)	5.2 (4.1)	4.9 (3.6)	0.31 (–0.56 to 1.18)	0.49	0.23 (–1.07 to 1.54)	0.72
NIHSS (/42)*	134	9.6 (7.2)	9.0 (7.4)	10.2 (7.1)	–0.05 (–1.42 to 1.32)	0.94	–1.19 (–3.64 to 1.26)	0.34
mRS (/6)*	134	3.9 (1.1)	3.7 (1.2)	4.1 (1.0)	0.53 (0.23 to 1.22)	0.14	0.49 (0.26 to 0.92)	0.028
BI (/100)*	134	36.2 (34.9)	41.3 (37.2)	29.8 (31.0)	1.57 (–3.60 to 6.73)	0.55	11.45 (–0.22 to 23.13)	0.055
Death (%)	141	2 (1.4)	1 (1.3)	1 (1.6)	…	…	0.81 (0.05 to 13.13)	0.88
12 wk								
DSRS (/12)*	124	4.2 (5.1)	4.4 (5.2)	3.9 (5.1)	1.01 (–0.44 to 2.46)	0.17	0.58 (–1.23 to 2.39)	0.53
EQ-5D as HUS (/1)*	113	0.02 (0.40)	0.08 (0.41)	–0.04 (0.39)	0.13 (0.00 to 0.27)	0.054	0.12 (–0.03 to 0.27)	0.11
EQ-VAS*	105	50.3 (30.7)	51.6 (30.1)	48.6 (31.7)	–4.17 (–15.22 to 6.88)	0.46	3.03 (–8.70 to 14.76)	0.61
Disposition (%)	141				0.66 (0.30 to 1.49)	0.32	0.63 (0.31 to 1.26)	0.19
Home		30 (21.3)	20 (25.6)	10 (15.9)	…	…	…	…
Institution		93 (66.0)	49 (62.8)	44 (69.8)	…	…	…	…
Died		18 (12.8)	9 (11.5)	9 (14.3)	…	…	…	…
Time to event								
Discharge (days)	141	28.2 (22.8)	27.7 (22.7)	28.7 (23.0)	–0.33 (–7.79 to 7.12)	0.93	–0.97 (–9.72 to 7.78)	0.83
Death (%)	141	18 (12.8)	9 (11.5)	9 (14.3)	1.11 (0.34 to 3.59)	0.86	0.79 (0.32 to 2.00)	0.62

BI indicates Barthel Index; DSRS, dysphagia severity rating scale; EQ-5D, European Quality of Life-5 Dimensions; EQ-VAS, European Quality of Life Visual Analogue Scale; HR, hazard ratio; HUS, health utility status; MD, mean difference; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and PES, pharyngeal electric stimulation.

*Includes death: NIHSS=43, DSRS=13, mRS=6, BI=–5, and HUS=0.

will have received a potentially therapeutic form of stimulation for 10 to 20 minutes (as compared with the 30+ minutes that patients randomized to active treatment receive). These potential explanations for the STEPS results have implications for the design of future trials of PES (and, indeed, other device trials) and training of investigators.

STEPS has several strengths, including the large sample size relative to previous studies of PES; generalizability because of wide inclusion criteria with both ischemic and hemorrhagic stroke, cortical, lacunar, and posterior syndromes, and a wide time window; recruitment from multiple countries in Europe; central concealment of treatment assignment; prospective collection of multiple aspiration, dysphagia, functional, and safety outcomes; and quality care in stroke units.

However, several limitations are also present. First, 195 patients were consented, 162 patients randomized but only 126 received at least 1 treatment session and had both a baseline and on-treatment PAS. Several factors explain this dropout, including withdrawal of consent and failure of insertion of the treatment catheter (Figure 1). A protocol amendment required that the treatment catheter had to be inserted before, and not after, randomization to reduce losses of patients who were randomized but could not be treated. Second, PES was delivered in 141 patients but 15 could not have VFS performed at both baseline and week 2 thereby excluding them from the primary analysis. Third, PES was given in a single-blind design with the patient but not treating person masked to stimulation. Some patients receiving active PES may have been aware of stimulation, whereas patients randomized to sham PES may have been aware of stimulation during threshold testing and possibly noticed that this was absent during the treatment sessions. Nevertheless, clinical outcomes measured at 2, 6, and 12 weeks were assessed by trained staff who were masked to treatment assignment and who were not involved in hospital care of enrolled patients. Furthermore, VFS images were adjudicated by radiologists or speech therapists who were similarly masked to randomized group.

In conclusion, we found that PES did not reduce radiological aspiration or clinical dysphagia. This result differs from a positive meta-analysis of previous small trials of PES in post-stroke dysphagia[12] and may result from several factors, including enrollment of patients with mild dysphagia, potential undertreatment with PES, and possible active stimulation of control patients. In view of this discrepancy, and the potential risk of overestimating treatment effect from smaller studies, further studies are planned in stroke patients with severe dysphagia or those requiring intensive care including ventilation.

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Disclosures

P.M. Bath received honoraria for work as the Chief Investigator and for consultancy. S. Hamdy is the inventor of PES and has stock in Phagenesis. J. Love was an employee of Phagenesis. Institutions using P. M. Bath, D. Cohen, H.K. Iversen, R. Dziewas, V. Woisard, and P. Clavé received per-patient fees for recruitment. P.M. Bath, P. Scutt, D. Cohen, H.K. Iversen, R. Dziewas, and V. Woisard received travel expenses for attending meetings. The other authors report no conflicts.

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Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial

Philip M. Bath, Polly Scutt, Jo Love, Pere Clavé, David Cohen, Rainer Dziewas, Helle K. Iversen, Christian Ledl, Suzanne Ragab, Hassan Soda, Anushka Warusevitane, Virginie Woisard and Shaheen Hamdy
on behalf of the Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPS) Trial Investigators

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SUPPLEMENTAL MATERIAL

Title
Pharyngeal electrical stimulation for treatment of dysphagia in subacute stroke: a randomised controlled trial (ISRCTN25681641)

Writing Committee
Philip M Bath, Polly Scutt, Jo Love, Pere Clavé, David Cohen, Rainer Dziewas, Helle K Iversen, Christian Ledl, Suzanne Ragab, Hassan Soda, Anushka Warusevitane, Virginie Woisard, Shaheen Hamdy

Trial Steering Committee
Philip M Bath (Nottingham, UK), Shaheen Hamdy (Manchester, UK), Conor Mulrooney (Manchester, UK), Jo Love (Manchester, UK).

Phagenesis Ltd (Manchester, UK)
Jo Love, Danny Green, Conor Mulrooney, David Drown, Jane Korby, Sian Scriven.

Data Monitoring Committee
Martin Dennis (Chair/Stroke Physician; Edinburgh, UK), Ian Ford (Biostatistician; Glasgow, UK), Susan McGowan (Speech and Language Therapist; London, UK).

Videofluoroscopy Adjudicators
Elizabeth Boaden (Moore, UK), Roger Newman (Preston, UK), Dana Hadley (Sheffield, UK)

SAE Adjudicator
Shaheen Hamdy (Manchester, UK)

Statistical analysis
Polly Scutt (Nottingham, UK).

Participating Countries and Sites
By country (number of randomising sites, participants) and sites (number of randomised participants): Principal Investigator, other Investigators †National Coordinator

Denmark (3, 17):
- Bispebjerg (2): P Meden, E Engemann, A Hansen, S Hamburg, L Ingemann, J Jansen, H Pedersen, S Rosenbaum, S Ulnits
- Glostrup (11): H Iversen †, S Andersen, S Eskildsen, V Fazilati, P Hornslet, S Jensen, B Langhorn, L Petersen, S Simonsen, D Skovgaard, H Sørensen, J Veng-Olsen, P Vögele, A West, T Wienecke
- Herlev (4): C Kruuse, D Hammer, C Hansen, L Molgård, L Nielsen, D Nørvang, V Petrovic, J Tybring

France (2, 7):
- Nantes (1): M Le Fort, O Bassard, A Chenet, E Cohen, P Hamon, B Hauraix, P Rapin
- Toulouse (6): V Woisard †, S Bodin, S Crestani, N Fenon, P Fichaux-Bourin, S Grand

Germany (4, 28):
- Bad Aibling (9): F Müller, C Ledl, J Doleschal, K Hinterberger, D Jungbluth, Y Knerr, M Lehmann, S Mudungaze, R Oldenburg, K Rieß, B Schäpers, M Schlutt, M Schumacher, K Trautwein
- Bad Neustadt (10): H Soda, B Behringer, S Fodor, A Friede, F Kasprsak, M Kirchner, A Märkert, R Weinhardt
- Bielefeld (1): W Schäbitz, S Basli, K Berends, B Berger, A Bienek, U Grage, C Hagemeister, N Jansen, A Sinning
- Münster (8): R Dziewas †, B Buerke, D Schulte to Bühne, C Hamacher, S Ölenberg, S Suntrup

Spain (1, 9):
- Mataró, Barcelona (9): P Clavé †, V Arreola, V Casado, I López, A Martín, L Mundet, D Muriana, E Palomeras, L. Rofes, N Vilardell

UK (10, 101):
- Essex (1): G Zachariah, V Biggs, K Blackmore, D Briggs, F Cairns, L Cooper, J Gunn, A Lyle, F McNeela, E Rafferty, S Smolen, K Swan, J Topliffe, V Umachandran, H Walsh, S Walsh, M Warwick
- Exeter (1): M James, A Bowring, N Chivers, R Evans, K Gupwell, G Guscott, S Hayes, S Keenan, H Kingwell, D Parsons, J Short, D Thomas
- Leicester (7): A Mistri, S Anand, P Christian, B Cole, M Dickens, D Everson, C Haunton, S Khan, L Manning, R Marsh, H McQueen, D Shaw
- London, Imperial (3): O Halse, S Amlani, L Bolton, D Brown, S Burkitt, E Catangui, K Collins, T Davies, J Godber, K Harrall, B Hazel, A Lacey, E Lawlor, T Sachs, J Slark, E Talbot, V Tilley, E Wackrow, S Wegecsanyi, L White, P Wilding, J Zimmerli
- Northwick Park (37): D Cohen, S Ackford, R Bathula, L Burgess, R Cave, C Cawley, S Condie, C Cowley, J Devine, M Macfarlane, M Mpelembue, E Tweedie, D Wood
- Nottingham (14): P Bath,† A Buck, J Clarke, P Cox, L Daunt, N Gilzeane, D Havard, JC Jobling, K Krishnan, S Rajakaruna, K Richardson, J Roffe, J Saunders, C Scottow, S Sheikh, F Shelton, L Wilkins
- Poole (18): S Ragab, D Broadbent, E Cowan, C Dickson, J Edington, L Gleave, A Grogan, E Jinks, J Legett, R Middle, U Naghotra, M Price, M Stevenson, L Sykes
- Stoke-on-Trent (15): A Warusevitane, A Barry, J Bee, C Bradbury, J Chenbala, L Dale, P Ferdinand, K Finney, J Grocott, J Hiden, J Lucas, S Lyjko, H Maguire, I Natarajan, M Richardson, C Roffe, R Sanyal, J Weerathunga
- Truro (2): F Harrington, K Adie, G Courtauld, D Gomes, A James, L Lucas, A Mate, P O'Brien, C Schofield, J Skewes, J Wright
- Wolverhampton (3): K Fotherby, N Ahmad, D Butler, C Cresswell, M Haley, K Jennings-Preece, F Lewis, D Morgan

Authors' contribution

All authors contributed to the interpretation of the results and writing of this report. As Chief Investigator, PMB prepared the protocol, supervised and reviewed the progress of the trial, recruited patients, and wrote the first draft of this report. JL prepared the protocol, and supervised and reviewed the progress of the trial.

Members of the writing committee supervised and reviewed the progress of the trial, and commented on the draft of this report. PS analysed trial data and commented on a draft of this report. All members of the writing committee have seen and approved the final version of this report.

Declaration of Interests

The trial was sponsored and funded by Phagenesis Ltd. PB received honoraria for work as the CI and for consultancy. SH is the inventor of PES, and has stock in Phagenesis. JL was an employee of Phagenesis. Institutions employing PB, DC, HKI, RD, VW, and PC received per patient fees for recruitment. PB, PS, DC, HKI, RD, and VW received travel expenses for attending meetings.

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This trial was funded by Phagenesis Ltd. We thank the investigators and research staff at the participating sites for their support, and acknowledge the support of the UK National Institute for Health Research, through the Stroke Research Network; recruitment in the UK would not have been possible without network support. PMB is Stroke Association Professor of Stroke Medicine.

SUPPLEMENTAL METHODS

Training of Investigators

All STEPS investigators were trained in the protocol, Good Clinical Practice, and use of the National Institutes of Health Stroke Scale, modified Rankin Scale (mRS) and Barthel Index. Investigators who delivered PES were trained in the technique.

Schedule for Monitoring of Sites and Data Integrity

Site monitoring was performed by trained Clinical research Associates who worked for Phagenesis Ltd or a delegated organisation. Their aim was to ensure quality control for the delivery of the protocol, collection of data and adherence with national regulations and ethics. Each recruiting site had a start-up visit for training, a monitoring visit after recruitment of the first patient, and a close-down visit; further visits were performed as deemed necessary by the Company. Monitoring visits confirmed the presence of the participant and their consent, eligibility criteria, 100% of data, and reporting of serious adverse events.

Central statistical monitoring of the data was performed according to Buyse *et al* [1] prior to locking of the data. Checks included logic and range checks, and digit preference. The monitoring procedures were compliant with the requirements of the sponsor, the national ethics committees and regulatory authorities in the participating countries, and fulfilled Good Clinical Practice requirements.

Sample Size Considerations

The primary endpoint for the study was change in mean penetration-aspiration scores (PAS) on the videofluoroscopy protocol, 2 weeks after treatment. The sample size was based on data gained from a phase II sham-controlled study.[2] In this study, the mean values of the change in mean PAS in the two randomised groups of sizes 16 and 12 were -1.4 and -0.1, giving an observed treatment effect of 1.3.The standard deviations in each group were 1.9 and 1.5 respectively. The distributions of values in each group were approximately normal, with standard deviation of 1.8.

Sixty patients in each group would provide 90% power to detect a difference of approximately 1.1 in the change in mean PAS, based on comparison of change in mean PAS between the two groups using a 2 sided t test, with alpha = 5%. The investigation was expected to provide higher power than this because the primary endpoint was adjusted for severity at baseline. To account for the loss of information caused by the potential for less than six swallows being available for every patient, and to account for patients dropping out before the two-week assessment, the sample size was increased by approximately 30%.

Therefore, 160 patients should be randomised in a 1:1 ratio between the treatment groups, this allowing for a one-in-six attrition rate at 2 weeks.

Independent Data Monitoring Committee (IDMC)
The IDMC was responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the intervention during the trial, assessing data integrity, and for monitoring the overall conduct of the trial. The IDMC *modus operandi* was defined in a charter. The IDMC reviewed the recruitment of patients, and assessed safety and efficacy measures by treatment group. The trial was reviewed on three occasions during the trial's recruitment period. The DMC was charged with informing the Trial Steering Committee if, at any time, the data showed evidence beyond reasonable doubt of a difference between the randomised groups in the primary outcome or for death. They also considered these data in the light of external information such as results from completed trials. One formal interim analysis was performed after 60 participants had been enrolled and completed the 2-week assessments. However, the DMC could perform statistical comparisons as they deemed necessary, with stopping criteria based on the Haybittle-Peto stopping rule (i.e. a difference of 3 standard errors is considered as clear evidence of a treatment effect). The study was not terminated early.

Inclusion and Exclusion Criteria
Screening Inclusion Criteria
- Subject is over 18 years of age
- Subject is suspected of having dysphagia
- Subject is able to comply with videofluoroscopy protocol
- Subject diagnosed with stroke, whether anterior or posterior circulation
- Subject has no previous history of dysphagia
- Subjects who are able to give voluntary, written informed consent to participate in the clinical investigation and from whom consent has been obtained/ or a consultee has consented on the subjects behalf in line with nationally agreed guidelines concerning adults unable to consent for themselves.
- Subject is not currently participating in any other interventional clinical study
- Subject is able to comply with CIP requirements
- Subject scores 0 or 1 on questions 1a of NIHSS

Randomisation Inclusion Criteria (post consent)
- Subject has confirmed dysphagia (PAS of 3 or more on VFS screening protocol)

Exclusion Criteria
- Subject stroke event was more than 42 days ago
- Subject is pregnant or a nursing mother
- Subject, in the opinion of the investigator, has advanced dementia
- Subject fitted with a pacemaker or implantable cardiac defibrillator

- Subject has unstable cardiopulmonary status (e.g. severe emphysema, heart failure)
- Subject has distorted oropharyngeal anatomy (e.g., pharyngeal pouch)
- Subject is dysphagic from conditions other than stroke
- Subject has been diagnosed with a progressive neurological disorder (e.g. Parkinson's disease, Multiple Sclerosis)
- Subject has a chronic medical condition that compromises cardiac or respiratory status (e.g. severe emphysema or heart failure that may render the insertion of the throat unsafe)
- Subject is receiving continuous oxygen treatment or the equipment for this is in place.

Patients in intensive therapy unit, whether intubated or not, were not included since many would require oxygen treatment.

Procedure for Videofluoroscopy (VFS, modified barium swallow)
VFS was performed by a trained and qualified speech & language therapist or radiologist; they had to comply with the STEPS VFS protocol and 'stop' criteria. A common VFS protocol was used across all participating sites. Strict adherence is required to this VFS protocol and the criteria to 'stop' the procedure as defined below.

Preparation
- The subject must remain nil by mouth for 60 minutes prior to the research VFS.
- The person delivering treatment/sham must not be present during the VFS.
- Capture a 'test frame' using the x-ray equipment to ensure all data will be captured.
- Ensure VFS study data is anonymised.
- Ensure use of lead numbers or annotation throughout the VFS to identify each trial clearly to the independent VFS analysers.
- Ensure use of the suprahyoid marker throughout the VFS procedure.
- Ensure the full swallow is recorded in a lateral view using continuous/25 or 30 frames per second screening, throughout.
- Ensure correct positioning of the subject throughout i.e. seat upright with a neutral head position.
- Ensure no use of swallowing strategies throughout e.g. head turns.

Specified Contrast Media
- The low osmolarity contrast media solution specified by Phagenesis will be used as the radiopaque contrast media during the STEPS VFS procedure.
- All volumes of contrast media will be measured accurately using a syringe.

VFS Protocol (see also appendix M):
- 6 trials of 5ml contrast media will be given to the subject from a small green Kapitex cup.
- Subjects will be asked to pour all of the contrast media into their mouth and then asked to swallow.
- 50ml contrast media will then be given in a 'normal' beaker and the subject asked to drink this sequentially.

Criteria to Stop the STEPS VFS Protocol:
Stop the VFS procedure immediately if any of the following occur:
Stage 1 (5ml trials)
- A PAS of 7 or 8 on 3 consecutive *bolus* trials.

Stage 2 (50ml trial)

- PAS score of 7 or 8 on 3 consecutive *swallows*.
- Initial occurrence of aspiration of more than 50% of the total bolus.

A 'Stop' may also be applied if 3 bolus trials have been complete and in the opinion of the staff conducting the VFS, the subject is unusually or unreasonably distressed, or if the subject becomes too unwell to continue.

A 'Stop' will NOT exclude the subject from the study.

VFS staff are asked to carry out the following actions in the event of the use of the stop criteria and/or significant aspiration.
- Prompt the subject to cough
- Prompt the subject to cough and swallow
- Refer the subject for chest physiotherapy as per local practice
- Arrange for the subject to be monitored over the next 24 hours as per local practice

The VFS images will be analysed off line by an independent panel of specialist SALTs who will respond with confirmation of the need for randomisation within 24 hours of screening VFS submission.

Outcome scales

Penetration aspiration scale [3]

Score	Description on videofluoroscopy
1	Material does not enter airway
2	Material enters airway. Remains above vocal cords & is ejected from airway
3	Material is above vocal cords & is not ejected from airway
4	Material enters airway, contacts vocal cords & ejected from airway
5	Material contacts the vocal cords & is not ejected from airway
6	Material passes below the vocal cords & is ejected into larynx or out of airway
7	Material passes below the vocal cords & is not ejected from the trachea despite effort
8	Material enters airway, passes below the vocal cords & no effort is made to eject the material

Dysphagia severity rating scale (DSRS) [2]
DSRS is a derivative of the dysphagia outcome and severity scale.[4]

Score	Fluids	Score	Diet	Score	Supervision
4	No oral fluids	4	Non oral feeding	4	No oral feeding
3	Pudding consistency	3	Puree	3	Therapeutic feeding (SALT/trained staff)
2	Custard consistency	2	Soft, moist diet	2	Feeding by third party (untrained)

1	Syrup consistency	1	Selected textures	1	Eating with supervision
0	Normal fluids	0	Normal	0	Eating independently

Statistics
Since a treatment could, in principle, be associated both with improved outcome and death, a sensitivity analysis was performed with death assigned a score one worse than the worst possible PAS (death = 9) and DSRS (13) scores; this is analogous to the mRS and EQ-5D-HUS which both include death in their scores (6 and 0 respectively).

Role of the funding source
The trial was overseen by the Chief Investigator (PB), PES Inventor (SH), and Trial Manager (JL), and run by the Trial Management Committee (PMB, SH, CM, JL), this including senior representatives of the funding and sponsoring company, Phagenesis Ltd (CM, JL). Sites received regular monitoring with 100% data verification. Data were collected using a commercial database (Rave, Medidata Solutions Inc.). Analyses were performed by PS at the University of Nottingham (PS). Interpretation and report writing were performed by the Trial Management Committee and National Coordinating Investigators. The corresponding author and another author (statistician PS) had full access to all the data in the study; additionally, the corresponding author had final responsibility for the decision to submit for publication, and is the guarantor for the study.

Amendments to clinical investigation

Version: date	Reason for Amendment	Countries affected
Final: 15/11/2011	Not actively used by sites – see amendment 1	France UK
1: 30/1/2012	• At request of UK REC - to include statement that clinical decision would take precedent • Clarify what will happen to data after 15 years	France UK
2: 19/9/2012	Non-substantial amendment: • Amendment to statement of conformity as now CE marked device. • Addition to the secondary objectives • Increased length of investigation to 18 months • Removed minimum and maximum site recruitment numbers • Increase in the number of sites • Clarification on treatment of patients according to local best clinical practice • Clarification of wording for VFS procedure Substantial amendment: • Addition to the secondary endpoints • Amendment to consent process at investigational sites in Germany • Addition of code-break procedure • Addition of safety reporting responsibilities	Denmark France Germany Spain UK
3: 6/6/2013	Non-substantial amendment: • Increased length of investigation • Increased number if investigation sites • Informed consent in non-UK sites to follow local practice and in line with country approvals.	Denmark France Germany Spain UK
4: 21/1/2014	Non-substantial amendment: • Increased length of investigation • Increased number of subjects from 140 to 160 • Clarify target population • Clarify speech & language therapist plan	Denmark France Germany Spain UK

VFS: videofluoroscopy

SUPPLEMENTAL TABLES

Supplementary Table I. Treatment dose and tolerance in 141 participants who received at least one treatment session. Treatment level is that actually received by patients randomised to pharyngeal electrical stimulation, or what patients randomised to sham would have received if actively treated.

	All	PES	Sham
Patients	141	78	63
Number of treatments	414	233	181
No. of treatments per patient	2.9	3.0	2.9
Threshold level (mA)	9.5 (6.2)	8.9 (5.1)	10.3 (7.4)
Range	1, 47	1, 30	1, 47
Tolerance level (mA)	16.9 (9.2)	16.7 (8.9)	17.3 (9.7)
Range	3, 50	4, 50	3, 50
Treatment level (mA)	14.8 (7.9)	14.5 (7.5)	15.1 (8.3)
Range	2, 50	2, 45	2, 50
Treatment – threshold (mA)	5.3 (5.3)	5.6 (5.6)	4.9 (5.0)
Range	-17, 27	-2, 27	-17, 26
Duration (minutes)	9.9 (1.2)	9.8 (1.4)	10.0 (0.7)
Range	0, 10	0, 10	0.2, 10
Undertreated (%) †	85 (60.7)	45 (58.4)	40 (63.5)

† Under-treatment is defined as patients with treatment <7.3 mA (mean - 1 standard deviation [5]) or treatment-threshold level <=0 mA.

Supplementary Table II. Penetration aspiration score (PAS), clinical and safety outcomes by treatment assignment (intention-to-treat) in patients who received at least one active or sham treatment and who had outcome measured. Data are number (%), median [interquartile range], or mean (standard deviation). Comparisons using multiple linear regression, ordinal logistic regression, Cox regression or binary logistic regression. Analyses were adjusted for site, age, NIHSS, feeding status, baseline PAS and baseline value; or unadjusted.

	N	All	PES	Sham	OR/HR/MD	2p adjusted	OR/HR/MD	2p unadjusted
PAS sensitivity analyses								
Mean of all boli (/9) †	126	3.7 (2.1)	3.7 (2.1)	3.7 (2.0)	0.24 (-0.32, 0.79)	0.40	0.04 (-0.67, 0.75)	0.91
Change ‡	123	-1.1 (1.8)	-1.2 (1.8)	-1.1 (1.8)	0.05 (-0.45, 0.54)	0.86	-0.05 (-0.67, 0.58)	0.89
Mean of all swallows (/8)	126	3.2 (1.8)	3.1 (1.8)	3.2 (1.8)	0.08 (-0.35, 0.50)	0.73	-0.07 (-0.70, 0.55)	0.82
Mean number of swallows	126	16.2 (8.7)	16.4 (9.9)	16.0 (7.0)	-0.23 (-2.66, 2.21)	0.86	0.43 (-2.62, 3.47)	0.78
Mean of first 3 boli (/8)	126	3.1 (2.2)	3.1 (2.2)	3.1 (2.2)	0.32 (-0.29, 0.92)	0.31	0.03 (-0.74, 0.79)	0.95
% of boli >3	126	40.0 (31.7)	39.6 (31.8)	40.4 (31.7)	3.47 (-8.14, 15.07)	0.56	2.06 (-11.66, 15.78)	0.77
Worst score (/8)	126	8 [5, 8]	8 [6, 8]	8 [4.5, 8]	1.99 (0.83, 4.78)	0.12	1.68 (0.84, 3.35)	0.14
2 weeks								
TOR-BSST, failed (%)	127	113 (89.0)	62 (88.6)	51 (89.5)	0.67 (0.08, 5.39)	0.71	0.91 (0.30, 2.80)	0.87
Feeding (%)	132				2.07 (0.97, 4.39)	0.059	1.42 (0.77, 2.63)	0.27
Oral, normal food		27 (20.5)	17 (23.3)	10 (16.9)				
Oral, soft diet		44 (33.3)	16 (21.9)	28 (47.5)				
Nasogastric tube		31 (23.5)	21 (28.8)	10 (16.9)				
PEG		11 (8.3)	7 (9.6)	4 (6.8)				
Other		19 (14.4)	12 (16.4)	7 (11.9)				
Weight (kg)	129	71.2 (15.3)	71.0 (14.7)	71.4 (16.1)	0.49 (-0.72, 1.69)	0.43	-0.34 (-5.63, 4.94)	0.90
BMI (kg/m^2)	127	25.0 (4.8)	25.4 (4.4)	24.4 (5.1)	0.23 (-0.20, 0.66)	0.29	1.00 (-0.64, 2.65)	0.23
MAC (m)	129	28.4 (4.2)	28.3 (3.7)	28.5 (4.8)	0.20 (-0.72, 1.11)	0.68	-0.22 (-1.66, 1.22)	0.77
Albumin (g/l)	105	36.8 (5.3)	37.0 (5.7)	36.6 (4.8)	-0.16 (-1.39, 1.08)	0.80	0.37 (-1.70, 2.44)	0.72
12 weeks								
TOR-BSST, failed (%)	103	75 (72.8)	42 (72.4)	33 (73.3)	0.88 (0.17, 4.41)	0.87	0.95 (0.40, 2.29)	0.92
HADS (/42)	92	11.5 (7.4)	11.0 (6.7)	12.1 (8.2)	1.80 (-0.97, 4.58)	0.20	-1.07 (-4.07, 1.93)	0.49
Weight (kg)	101	73 (14.9)	72.1	74.1	0.56 (-1.02, 2.14)	0.49	-1.97 (-7.80, 3.85)	0.51

			(14.3)	(15.8)				
BMI (kg/m^2)	98	25.5 (4.6)	25.6 (4.2)	25.4 (5.0)	0.37 (-0.19, 0.94)	0.20	0.25 (-1.56, 2.06)	0.79
MAC (m)	104	28.3 (3.6)	27.9 (3.5)	28.7 (3.7)	-0.05 (-0.83, 0.72)	0.89	-0.79 (-2.18, 0.60)	0.27
Albumin (g/l)	62	41.4 (5.2)	41.7 (4.6)	41.1 (6.0)	-0.28 (-1.83, 1.27)	0.73	0.63 (-1.96, 3.23)	0.63
Disposition (%)	141				0.66 (0.30, 1.49)	0.32	0.63 (0.31, 1.26)	0.19
Home		30 (21.3)	20 (25.6)	10 (15.9)				
Institution		93 (66.0)	49 (62.8)	44 (69.8)				
Died		18 (12.8)	9 (11.5)	9 (14.3)				

† Includes death: PAS=9; ‡ All treatments received (N=123)

BMI: body mass index; MAC: mid arm circumference; TOR-BSST: Toronto Bedside Swallowing Screening Test

Supplementary Table III. Participants in the safety population (N=152) with one or more serious adverse events (SAE) up to 12 weeks; no serious adverse device effects (SADE) occurred. Data are number (%) for total and fatal events. Comparison by unadjusted binary logistic regression.

	Any				Fatal			
	All	PES	Sham	P	All	PES	Sham	p
Patients	152	85	67		152	85	67	
Cardiac	9 (5.9)	6 (7.1)	3 (4.5)	0.73	4 (2.6)	2 (2.4)	2 (3.0)	1.00
Gastrointestinal	2 (1.3)	2 (2.4)	0 (0)	0.50	0 (0)	0 (0)	0 (0)	-
General	3 (2.0)	0 (0)	3 (4.5)	0.083	3 (2.0)	0 (0)	3 (4.5)	0.083
Hepatobiliary	1 (0.7)	1 (1.2)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	-
Infections	11 (7.2)	6 (7.1)	5 (7.5)	1.00	4 (2.6)	2 (2.4)	2 (3.0)	1.00
Investigations	1 (0.7)	1 (1.2)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	-
Neoplasms	1 (0.7)	1 (1.2)	0 (0)	1.00	1 (0.7)	1 (1.2)	0 (0)	1.00
Nervous system	8 (5.3)	4 (4.7)	4 (6.0)	0.73	4 (2.6)	3 (3.5)	1 (1.5)	0.63
Renal/urinary	2 (1.3)	1 (1.2)	1 (1.5)	1.00	0 (0)	0 (0)	0 (0)	-
Respiratory	8 (5.3)	5 (5.9)	3 (4.5)	1.00	2 (1.3)	1 (1.2)	1 (1.5)	1.00
Surgical/medical	2 (1.3)	2 (2.4)	0 (0)	0.50	0 (0)	0 (0)	0 (0)	-
Total SAEs	40 (26.3)	22 (25.9)	18 (26.9)	1.00	18 (11.8)	9 (10.6)	9 (13.4)	0.62
Total SADEs	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	

By 2 weeks, SAE rates were: Total 13 (9.2%), PES 7 (9.0%), Sham 6 (9.5%) (2p=0.91)
No SAEs were recorded as probable or possibly related to treatment
No Serious Adverse Device Effects (SADE) were recorded

Supplementary Table IV. Treatment operator assessment of ease of use of device in 162 randomised patients across both treatment groups. Data are numbers of patients (%).

	Difficult
Provision of treatment	3 (2.2)
Meet infection control guidelines	0 (0)
Placement of catheter	10 (7.5)
Passing catheter (as NGT)	44 (33.1)
Secure catheter	19 (14.3)
Training to deliver treatment	3 (2.7)

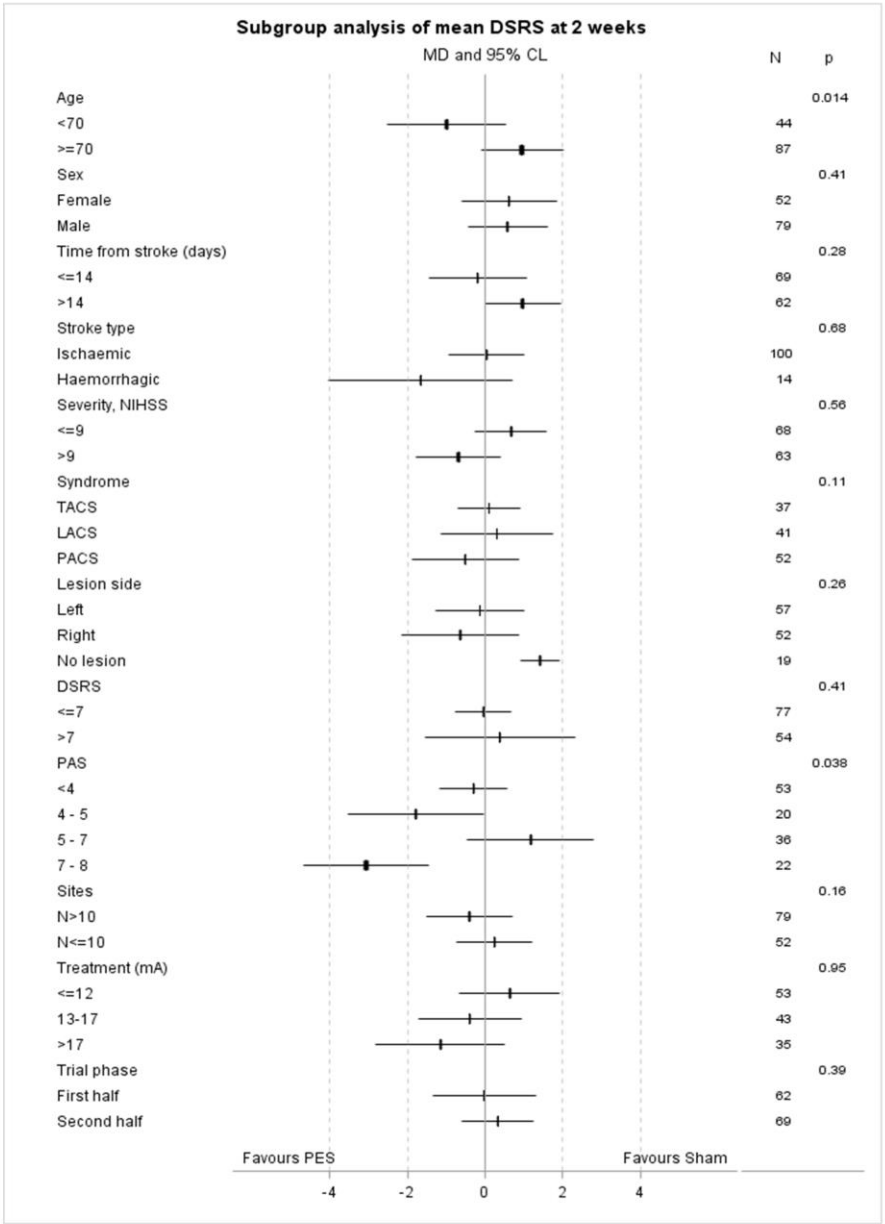
Supplementary Table V. Penetration aspiration score (PAS) and dysphagia severity rating scale (DSRS) before and after treatment in the active and sham groups in four trials of pharyngeal electrical stimulation. Patients with both baseline and 2 week mean PAS are included. Data are unadjusted PAS and DSRS mean scores or differences.

Group	Timing	PAS				DSRS			
		Trial 1 [2]	Trial 2 [2]	Trial 3 [6]	STEPS	Trial 1 [2]	Trial 2 [2]	Trial 3 [6]	STEPS
Active	Before	4.8	4.6	4.5	4.8	ND	6.4	7.8	7.7
	After	3.7	3.2	2.6	3.6	ND	2.5	4.4	5.0
	Δ	-1.0	-1.4	-1.9	-1.1	ND	-3.9	-3.4	-2.7
Sham	Before	4.3	3.9	3.9	4.7	ND	5.6	6.8	6.8
	After	4.8	3.8	4.3	3.6	ND	4.8	5.0	4.8
	Δ	+0.5	-0.1	+0.4	-1.1	ND	-0.8	-1.8	-2
Active-sham	Δ	-1.5	-1.3	-2.3	0	ND	-3.0	-1.5	-0.6
	p	0.017	0.061	0.22	1.00	ND	0.11	0.11	0.25

ND: Not done

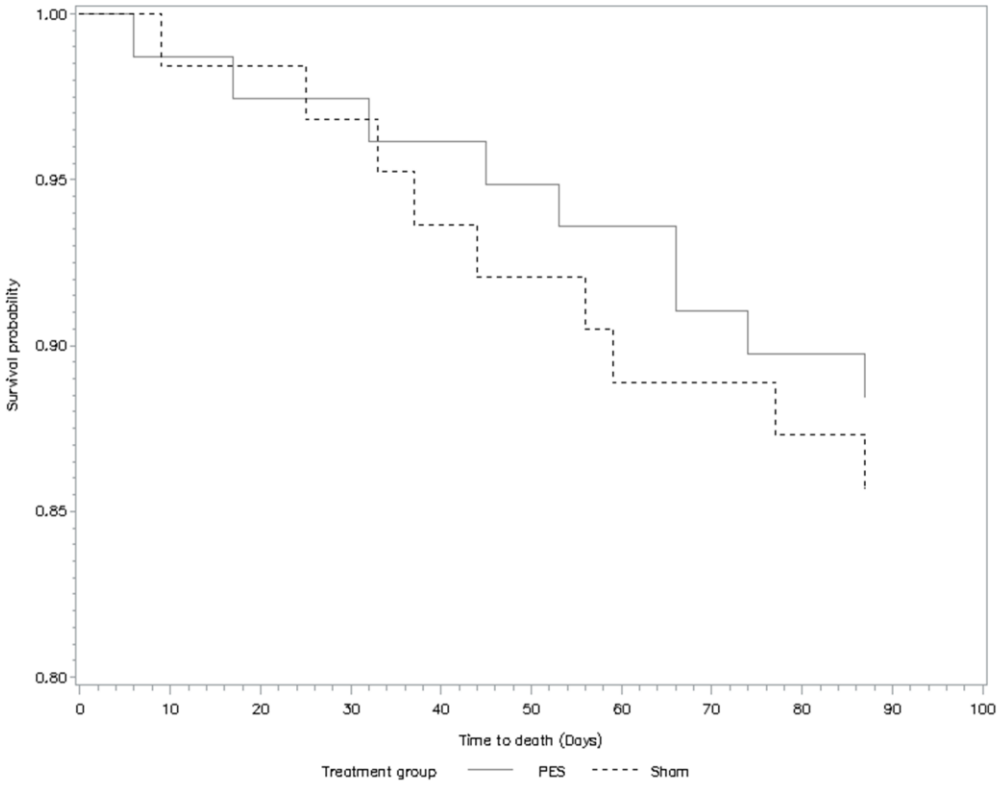
SUPPLEMENTAL FIGURES

Supplementary Figure I. Effect of treatment on dysphagia severity rating scale in 131 patients at 2 weeks in pre-specified subgroups determined at baseline. Analysed with multiple linear regression adjusted for baseline PAS, stratification variables (site, feeding status) and prognostic baseline variables (age, baseline PAS, NIHSS).

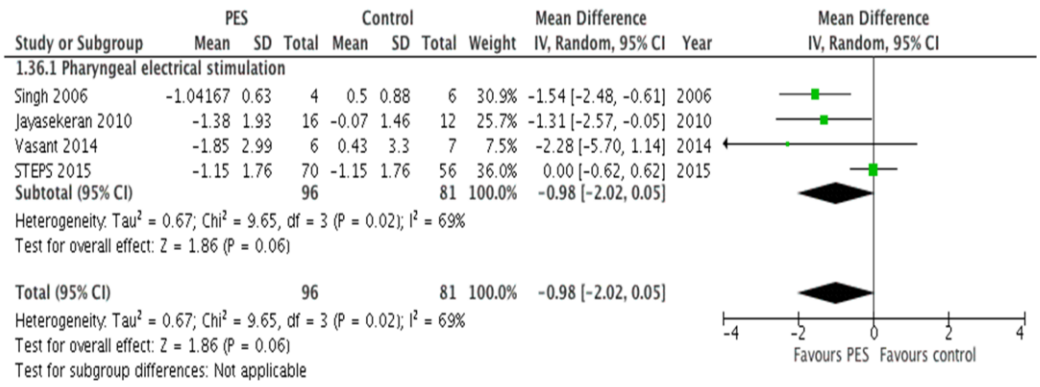


The black squares represent point estimates for the mean difference, and the horizontal lines represent 95% confidence intervals. The rectangle incorporates the point estimate and the 95% confidence intervals of the overall effects within categories. P values are for the interaction between subgroup and allocated treatment.

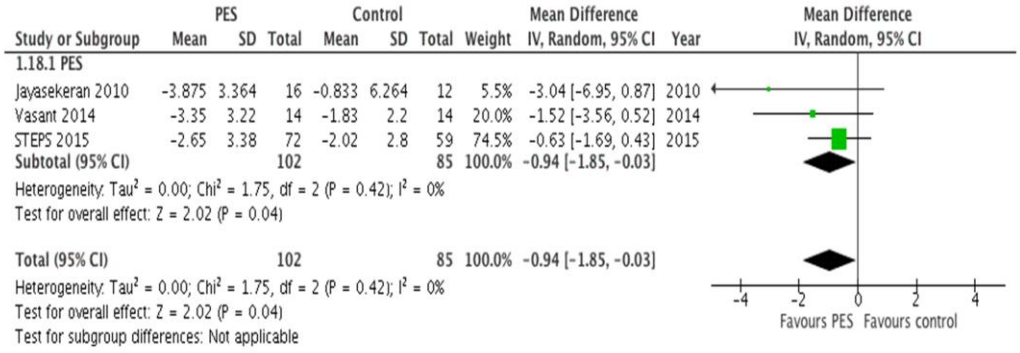
Supplementary Figure II. Survival of patients randomised to pharyngeal electrical stimulation (PES) versus sham. Adjusted hazard ratio 1.11 (0.34,3.59), p=0.86 (n=141).



Supplementary Figure III. Meta-analysis of the effect of pharyngeal electrical stimulation (PES) on radiological aspiration at two weeks, as assessed using the penetration aspiration score (PAS). Three previous trials and the present trial are included. Data are mean change in PAS, with 95% confidence intervals, using a random effects model.



Supplementary Figure IV. Meta-analysis of the effect of pharyngeal electrical stimulation (PES) on clinical dysphagia at two weeks, as assessed using the dysphagia severity rating scale (DSRS). Two previous trials and the present trial are included. Data are mean change in DSRS from baseline, with 95% confidence intervals, using a random effects model.



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咽部电刺激治疗亚急性卒中伴发吞咽障碍

一项随机对照试验

Pharyngeal Electrical Stimulation for Treatment Of Dysphagia in Subacute Stroke

A Randomized Controlled Trial

Philip M. Bath, DSc, FMedSci; Polly Scutt, MSc; Jo Love, BSc; Pere Clavé, MD, PhD; David Cohen, FRCP; Rainer Dziewas, MD, PhD; Helle K. Iversen, MD, DMSci; Christian Ledl, MA; Suzanne Ragab, FRCP, MPhil; Hassan Soda, MD, PhD; Anushka Warusevitane, MRCP(UK); Virginie Woisard, MD, PhD; Shaheen Hamdy, FRCP, PhD; on behalf of the Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPS) Trial Investigators

背景和目的：卒中后吞咽障碍很常见，与死亡及照料依赖的增加相关，而治疗方法有限。咽部电刺激（pharyngeal electric stimulation，PES）是一种新的治疗卒中后吞咽障碍的方法，这种方法经过 3 项试验性的随机对照试验，显示出了良好的应用前景。

方法：将 162 例近期患有缺血性或出血性卒中并伴有吞咽障碍的患者 [视频荧光透视下的误吸评分（Penetration Aspiration Score，PAS）≥ 3）] 随机入组到 PES 治疗组或假治疗组，连续治疗 3 d。主要观察指标是吞咽安全性评估，于 2 周时采用 PAS 评分进行评估。次要观察指标包括吞咽障碍严重程度、吞咽功能、生活质量和严重不良事件，于 6 周和 12 周时进行评估。

结果：在随机分配的患者中，平均年龄 74 岁，男性占 58%，缺血性卒中占 89%，PAS 值为 4.8。治疗中使用的平均电流是 14.8（7.9）mA，持续时间为每阶段 9.9（1.2）min。在之前获得数据的基础上，随机分配到 PES 治疗组的患者中的 45 例（58.4%）似乎并未接受最适刺激量。2 周时的已校正基线的 PAS 值在随机分配的两组中差异无显著性：PES 治疗组 3.7（2.0），假治疗组 3.6（1.9），*P*=0.60。同样，次要观察指标差异亦无显著性，包括临床吞咽和功能的结局。无严重的仪器设备相关的不良事件发生。

结论：对于亚急性卒中伴有吞咽障碍的患者，PES 治疗方法是安全的，但并不能改善吞咽障碍。患者接受 PES 治疗量不足可能导致了这种中性结果。

关键词：吞咽障碍；咽部电刺激；随机对照试验；卒中

（Stroke. 2016;47:1562-1570. 天津医科大学总医院神经内科 王菲 译 程焱 校）

急性卒中患者有 50% 伴有口咽部吞咽障碍，其中多达 40% 的患者在一年后仍有吞咽障碍[1]。吞咽障碍并发误吸、肺炎及营养不良[2]，这些患者需要通过鼻饲管或经皮内镜引导胃造瘘管进行肠内营养，通常需要长期的专业护理[3]。尽管可以使用一些物理和行为技术治疗吞咽障碍，但是仍没有十分明确的治疗方法[4]。

人类吞咽功能由双侧大脑半球皮质支配区所控制（与惯用手无关）[5]。吞咽障碍经常发生在控制吞咽的皮质区卒中之后，并在卒中再发时加重。吞咽功能依靠支配咽部的延髓颅神经的传入反馈，增强咽部的感觉传入使皮质吞咽控制产生长时间有利的变化[6]，这个过程是通过吞咽皮质区功能相关的重构而实现的[6,7]。

在咽部电刺激（pharyngeal electric stimulation，PES）的发展过程中，一项以健康受试者为对象[8,9]的研究表明，PES 方法的实施应采用 5 Hz 频率、时长为 10 min、电流为阈电流值加阈电流值与耐受水平差值的 75% 的电流值，耐受值是对脑兴奋性有最大影响的数值[8,10]。在一项随机剂量对照试验中，给予亚急性卒中患者 PES 治疗，PES 减少了放射性误吸，表现为误吸评分（Penetration Aspiration Score，PAS）值的下降[9]。同样，在空白对照平行组Ⅱ期试验中，卒中后吞咽障碍的患者给予 PES 治疗，也降低了临床吞咽障碍 [应用吞咽障碍严重程度评定量表（Dysphagia Severity Rating Scale，DSRS）进行评估] 和住院时间[9]。在一个远期的多中心Ⅱ期随机空白对照试验中，PES 方法对于减少临床吞咽障碍症状和减少住院时间并没有明显的作用[11]。在这 3 项试验的个体患者数据的 meta 分析中发现，PES 显著地降低了误吸（PAS）和吞咽障碍（DSRS），安全并且患者耐受较好[12]。本研究报道一项亚急性卒中后伴有吞咽障碍的患者给予 PES 治疗的大规模、随机、空白对照的Ⅲ期试验。

材料与方法

研究对象

本试验有如下特点：国际化、多中心、随机化、空白对照、患者设盲、结果评估人员设盲、设立平行组，详情请见在线补充数据。简而言之，即近期发生过卒中并且视频荧光透视（videofluoroscopy，VFS）确定的吞咽障碍患者，随机被分配到 PES 治疗组或假治疗组，治疗 3 d。主要观察指标是 PAS 值，第 3 个疗程结束后 2 周用 VFS 进行评估。

符合以下条件的患者可以进入后续试验：由于缺血性或出血性卒中引起临床出现卒中症状被送往医院、年龄 18 岁及以上、床旁测试确定有临床吞咽障碍（一位护士或语言治疗师使用本地方法评估，通过

Correspondence to Philip M. Bath, DSc, FMedSci, Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, United Kingdom. E-mail philip.bath@nottingham.ac.uk

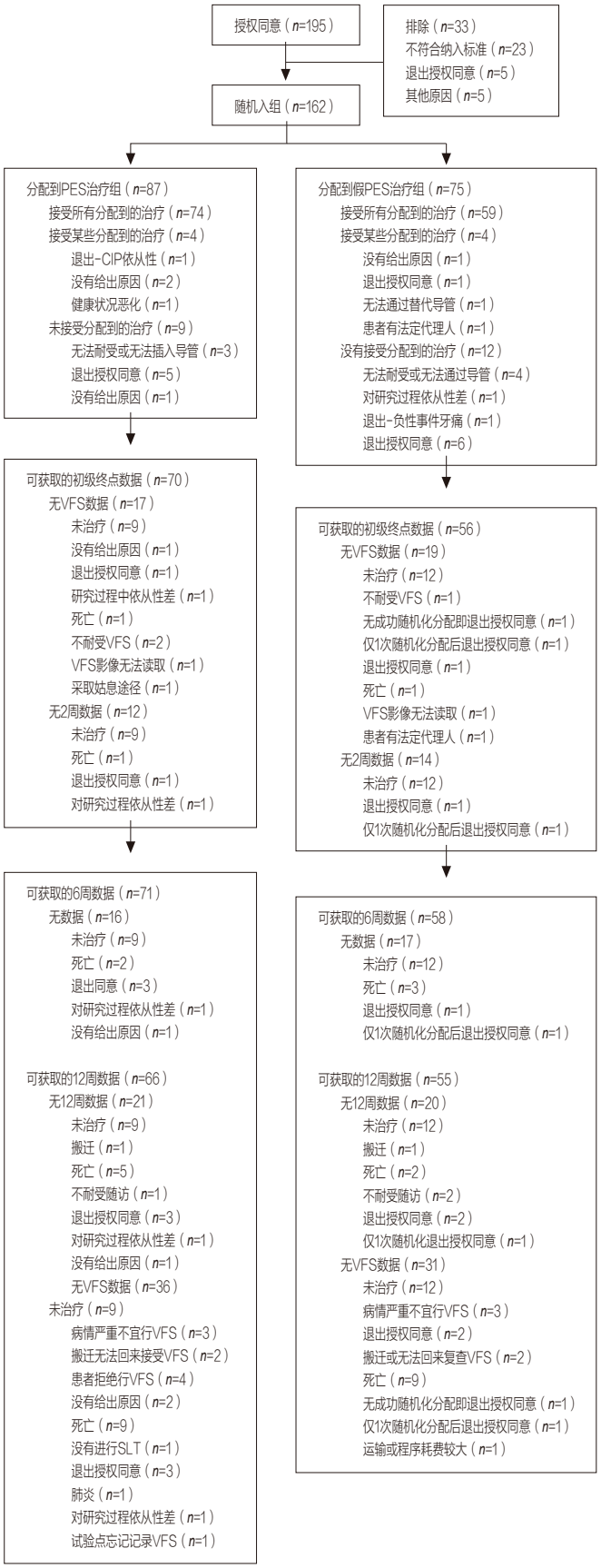

图1 本试验的患者入组情况：同意195例；采用VFS透视者181例；随机分配入组162例；拟治疗152例；实施治疗141例；治疗患者中进行2周VFS评估126例；接受3次治疗并进行2周VFS评估123例；进行12周VFS评估95例。注：AE：负性事件；CIP：临床研究计划；Rx：随机化；SLT：语言治疗；VFS：视频透视。

多伦多床旁吞咽测试法进行确认）、处于清醒状态[美国国立卫生研究院卒中量表（National Institutes of Health Stroke Scale，NIHSS）问题1a的评分为0或1]、至少有一次（应用VFS评估）PAS评分≥3（见在线补充数据的描述）[13]，并且在卒中发病42 d内可以治疗。在入院后入组前，应用计算机断层扫描（computed tomography，CT）或磁共振（magnetic resonance imaging，MRI）标准成像技术，确诊是缺血性卒中亦或出血性卒中。主要的排除标准包括：吞咽障碍病史、吞咽障碍由非卒中因素引起、进行性痴呆、植入起搏器或原位除颤器、不稳定的心肺状态或是有病变的循环或呼吸状态、口咽部解剖畸形、有进行性神经系统障碍的附加诊断、持续接受氧疗、孕妇或哺乳期妇女。

伦理和审批

本研究得到了各参与国家及地区的伦理委员会和主管部门的批准，被英国国立健康研究卒中研究院接受。按照国家相关规定，在注册登记之前，已获得每位患者的知情同意书，在患者无法自主决定时（如因吞咽障碍或意识模糊），由家属代理同意；在德国Bundesamt für Strahlenschutz管理机构不允许代理同意。试验由试验管理委员会实施（P.M.B., S.H., C.M., and J.L.）。独立的数据监测委员会将每6个月查看一次原始实验数据。本试验的注册编号为ISRCTN25681641。

随机设计

确定存在吞咽障碍（PAS ≥ 3）后，采用VFS（见下文）作为研究方法进行评估[14]。研究人员将基线和后续数据输入一个商业数据库（Rave, Medidata Solutions, Inc），这个数据库与一个随机化的列表（Quantics Consulting, Ltd）相关联。对数据进行检查以确定患者的资格，然后系统按照分配比例为1:1，指派一个参与者进入PES治疗组或假治疗组。分配方式是根据随机排列区块(大小为6)，采用进食方式（有或无人工喂养）进行分层，以加强组间的平衡。

视频荧光透视

在每个受试点，语言治疗师或放射科医生按照当地操作流程，来实施VFS。在每一个时间点（基线、第2周和第12周），给每个受试者至多6×5 ml小团造影剂饮料（英国是Omnipaque 300，法国是Visipaque 270或Accupaque 300），液体浓度（≈ 40% wt/vol）。然后给受试者饮用50 ml造影剂，并记录其吞咽情况。

在基线时，3项阳性才会使用小团造影剂饮料（即至少一次吞咽一团以内PAS ≥ 3者），只要达到要求，就不再给更多的小团造影剂饮料，这样可以降低误吸和肺炎。之后给予3~7个小团造影剂饮料（每个诱导至少一次吞咽）。完成之后，立即将每次给予小团造影剂饮料引发吞咽的高质量数码VFS影像文件传送给两位独立裁定员中的一位，一位裁定员对临床信息完全不知道，另一位裁定员确认患者是否符合吸入造影剂的纳入标准。数码VFS的使用降低了文件传送过程中的图像失真。确认接受患者后，就可以开始进行治疗。第2周和12周的VFS影像都同样上传，交由对患者详细情况和随机化设计完全不知道的那位裁定员予以评估。静态误吸是指在视频文件上、声音辅助或是监测仪检测的不伴有咳嗽的误吸。

操作流程

经过消毒的一次性治疗导管（Phagenyx，Phagenesis，Ltd，英国曼彻斯特）包含一个用于鼻饲的内部管腔，由操作员将导管经患

表 1 随机入组人群的基线特征

	人数	随机入组	PES 治疗	假治疗
患者	162	162	87	75
年龄，岁	162	74.4（11.2）	74.0（9.9）	74.9（12.6）
性别，男性（%）	162	94（58.0）	48（55.2）	46（61.3）
种族（%）	162			
亚裔		15（9.3）	9（10.3）	6（8.0）
黑种人		4（2.5）	0（0.0）	4（5.3）
白种人		139（85.8）	74（85.1）	65（86.7）
其他		4（2.5）	4（4.6）	…
量表评分（/6）	153	4.0（1.1）	3.9（1.1）	4.1（1.2）
Barthel 指数（/100）	153	28.4（29.8）	32.4（31.7）	23.8（26.8）
卒中，既往卒中（%）	162	23（14.2）	15（17.2）	8（10.7）
影像可见（%）	161	42（26.1）	25（28.7）	17（23.0）
卒中类型（%）	161			
缺血性 / 正常		143（88.8）	77（89.5）	66（88.0）
脑内出血性		17（10.6）	9（10.5）	8（10.7）
无卒中		1（0.6）	0（0）	1（1.3）
CT 中病变侧（%）	158			
左侧		63（39.9）	33（38.4）	30（41.7）
右侧		69（43.7）	36（41.9）	33（45.8）
无病变		26（16.5）	17（19.8）	9（12.5）
症状（%）	157			
全前循环		41（26.1）	21（24.4）	20（28.2）
部分前循环		69（43.9）	44（51.2）	25（35.2）
腔隙性		46（29.3）	21（24.4）	25（35.2）
后循环		1（0.6）	0（0.0）	1（1.4）
严重，NIHSS（/42）	152	9.9（6.4）	9.6（6.5）	10.2（6.2）
言语障碍，NIHSS（%）	152	55（36.2）	29（35.8）	26（36.6）
发病 - 随机入组天数（d）	162			
平均值（SD）		13.4（9.7）	12.6（9.5）	14.4（10.0）
中位数（IQR）		11（6~18）	10（5~17）	12（6~21）
DSRS（/12）	154	7.6（3.8）	8.0（3.9）	7.0（3.5）
TOR-BSST，失败（%）	162	158（97.5）	85（97.7）	73（97.3）
进食方式（%）	162			
经口，普食		10（6.2）	5（5.7）	5（6.7）
经口，软食		45（27.8）	23（26.4）	22（29.3）
经鼻饲		90（55.6）	52（59.8）	38（50.7）
PEG		4（2.5）	3（3.4）	1（1.3）
其他		13（8.0）	4（4.6）	9（12.0）
体重（kg）	153	71.9（16.4）	71.9（15.3）	72.0（17.6）
体质指数（kg/m^2）	148	25.2（5.0）	25.7（4.8）	24.7（5.2）
臂中围（cm）	143	28.3（3.6）	28.2（3.7）	28.5（3.6）
白蛋白（g/l）	144	36（5.7）	36.4（5.8）	35.5（5.6）
胸部感染（%）	156	8（5.1）	3（3.6）	5（6.9）
渗透误吸评分（/8）	162	4.7（2.0）	4.7（2.1）	4.7（1.9）
PAS>2	162	148（91.4）	79（90.8）	69（92.0）

注：表中数据代表数值（%）、中位数（IQR：四分位数间距）或均值（SD：标准差）。CT：计算机断层扫描；DSRS：吞咽障碍严重程度评分；NIHSS：美国国立卫生研究院卒中量表；PAS：渗透误吸评分；PEG：经皮内镜胃造瘘术；TOR-BSST：多伦多床旁吞咽功能筛查试验。

者的鼻腔插入。插入的部分末端距离口腔的长度与患者的身高有关，这样就可以使位于导管外表面的一对环状治疗电极能靠近咽部。

经 VFS 确诊为吞咽障碍后可以立即进行治疗，每日进行并连续治疗 3 d[9]。在每个疗程中，将导管与控制基座相连，将电流频率调至 5 Hz，然后逐渐由 1 mA 调高到可检测的阈值（患者开始意识到刺激），然后调到所有患者的耐受电流强度水平（患者不能忍受更高的电流时）。随机分配到 PES 治疗组的患者采取上述实施过程，使用治疗电流量（mA）阈值加阈值与耐受水平差值的 75%，时长为 10 min；这个模式在之前的 PES 研究中已经成功地使用过，并且被认为是采用了一个并不太接近耐受水平的有效刺激电流水平[12]。被随机分配到假治疗组的患者，在建立阈值和耐受值之后并未给予电刺激。在这个过程中患者是完全不知道治疗分配安排的，而治疗研究人员并不设盲。如果患者由于安全性的原因退出治疗，或是出现不可接受的不良事件，则治疗停止。

PES 治疗组和假治疗组都给予标准化卒中护理，包括住院期间给予溶栓及康复治疗。所有患者系统地应用降压药、口服抗血栓药和降血脂药，在每一个试验点治疗中的二级预防过程中，也推荐施行颈动脉内膜切除术（对于缺血性卒中的患者）。出院时会有最终确定的诊断，诊断是基于临床表现和神经系统影像检查得出的。

观察指标

主要观察指标检测是在 2 周时用 VFS 方法评估造影剂误吸的 PAS 值[14]。3 项测试研究中均在 2 周时应用 VFS 评估[12]。作为次要观察指标，在 12 周时应用 PAS 进行评分。

在第 2、第 6 和第 12 周出现的其他预先设定的次要指标包括：临床吞咽障碍（DSRS[9]；参考在线补充数据）、依赖性 [改良 Rankin 量表（modified Rankin Scale，mRS）[15,16]]、日常生活能力 / 障碍（Barthel 指数[17]）、功能障碍（NIHSS[18]）、健康相关的生活质量 [欧洲生活质量 -5 维（European Quality of Life-5 Dimensions，EQ-5D）[19]] 和营养程度测量（体重、手臂中部周径、血白蛋白）。从最初入院到出院时，调查人员记录住院时间和出院后去向（转院或是回家）。

安全性观察指标包括以下内容：所有原因病死率和特殊原因病死率；严重不良事件和严重的仪器引起的不良事件；胸部感染或肺炎的情况（采用局部诊断，因为关于胸部感染和肺炎的诊断不完全确定[20]）。

中心研究组的一位对于治疗分配完全不知情的成员，对调查人员上报的严重不良事件进行确认和分类，其中包括特定原因导致的死亡。未接受入组治疗或未坚持按步骤治疗的患者，也都进行了随访。招募中心派出一位对治疗分配完全不知情的研究人员分别在第 2、第 6 和第 12 周治疗后进行随访。

统计学分析

在数据未公开之前，数据分析结果发布在 Phagenesis 公司网站上，http://www.phagenesis.com/wp-content/uploads/2012/09/Statistical-Analysis-Plan-STEPS.pdf（March 21，2012）。试验计划招募 140 例患者以检测出 PAS 变化（所有可用丸饮剂引起吞咽的平均值），处理组间从基线到 2 周的变化为 1.1 点（标准差为 1.8），效能 90%，双边界值 5%，允许有 15% 患者随访的数据不全或丢失。在 3 项试验患者个体数据分析之后[12]，初步分析转为治疗组之间可用每 3~7 个小团造影剂饮料最差吞咽的均值比较（调整为相同的基线，无数据缺失），因为这样在统计学上更真实可靠并与临床更为接近，是数据揭盲前的决定。

按照以下原则创建 4 个分析群：随机化，即所有人被分配到 PES

治疗组或假治疗组；安全性，即所有随机分配的患者都尝试进行治疗，不论是否施行 PES 治疗都进行导管插入；有效性，即所有随机分配的患者都接受至少一个阶段的 PES 治疗或假治疗，并且计算所有患者的基线和 2 周时的初级结果（PAS 值）；操作流程化，即随机分配的患者接受所有 3 项治疗，并且计算所有患者的基线和 2 周时的 PAS 值。

应用多次线性回归方法，调整治疗中的 PAS 值至基线 PAS 值、分层变量（试验点和进食状态）、预后基线变量（年龄、性别、NHISS），来对比分析各治疗组之间的吞咽状态。次级结果分析使用的是：多次线性回归（针对连续性数据，例如 EQ-5D）、有序 logistic 回归（有序分类数据，例如 mRS）、二元 logistic 回归（二次分类数据，例如 PAS ≤ 3、严重负性事件、胸部感染）以及 Kaplan-Meier 和 Cox 回归模型。95% 的可信区间，P<0.05 被认为差异有显著性。分析过程使用的是 SAS 软件（版本 9.3）。进行总结的 meta 分析是基于咽部电刺激治疗吞咽障碍的组数据（Swallowing Treatment Using Pharyngeal Electrical Stimulation，STEPS）和更早的研究[9,11]，使用 Cochrane Collaboration's Review Manager 软件（版本 5.3）。

附加信息

关于材料与方法的其他详细信息见在线补充数据。

结果

2012 年 4 月 -2014 年 9 月，选取 195 例患者进行试验；用 VFS 观察了 181 例患者；对 162 例患者分配治疗（随机人群）；对 152 例患者尝试进行治疗（安全群体）；实际治疗 141 例患者（至少给予 1 个疗程的 PES 治疗或假治疗）；获得了 126 例患者的 2 周 VFS 结果（初级结果群体）；获得 95 例患者的 12 周 VFS 结果（图 1）。进入试验和随机分配入组的患者人数之间的差别包括：VFS 透视结果显示误吸阴性者、导管插入失败者和治疗后 2 周无 VFS 结果的患者。162 例随机分配入组的患者来自 5 个国家（丹麦、法国、德国、西班牙和英国，见在线补充数据）的 20 个试验点招募而来；这其中 87 例患者被分配到 PES 治疗组，75 例患者被分配到假治疗组（图 1）。101 例患者（62.3%）招募自英国。随机分组的基线平衡性良好（表 1）：平均年龄 74 岁（标准差为 11），94 例为男性（58%），143 例患者曾有缺血性卒中（89%）。从发生卒中到被随机分组的时间平均为 13（10）d。数据监测委员会回顾了 3 次试验，每次都建议试验应继续进行。

得到至少 1 个疗程治疗的参与者 141 例，对于分配到 PES 治疗组或假治疗组的依从性良好。有 15 例接受治疗的参与者没有 2 周的 VFS 结果，有 126 例接受治疗的参与者有 2 周的 VFS 结果，这两种情况的基线情况并没有明显差异。随机分配到假治疗组的患者都没有接受 PES 治疗，所有接受插管并且随机分配到 PES 治疗组的患者均接受了至少一个疗程治疗。PES 治疗组的平均治疗刺激电流是 14.5 mA，平均处理时长是 9.8 min，平均治疗次数是 3.0（见在线补充数据表Ⅰ）。然而目前水平恰当治疗的证据似乎存在：58% 的 PES 治疗患者的治疗电流水平 < 10.2 mA（从既往研究中选择的数值 12），治疗电流值水平与阈值水平相同，或治疗电流值水平低于阈值水平。

在主要观察指标数据中，平均 PAS 的基线为 4.8（标准差为 2.0），在 2 周时 2 组的 PAS 值均有所下降（表 2）。按照年龄、试验点、NHISS、基础进食状态和 PAS 值进行调整，2 周的 PAS 差异并无显著性，平均差异为 0.14（95% 可信区间，-0.37~0.64；P=0.60；表 2 和图 2）；基线到 2 周 PAS 值的平均变化值在 2 组之间差异并无显著性：PES 治疗组 -1.2（1.8）对应假 PES 治疗组 -1.2（1.8），差异为 0.14（-0.37~0.64）。之前的研究对于个体患者数据的 meta 分析表明，不同统计方法在统计学有效性上是不同的 12；在灵敏度分析中，使用不同的统计学方法评估时（见在线补充数据表Ⅱ），PAS 值在各组之间差异并无显著性。当在预先设定的亚组群中评估时，并未出现有意义的相互作用（图 2）。

PES 对于后续吞咽状态和进食方式并无明显效果，吞咽状态和进食方式包括 12 周的造影剂误吸（PAS）、2 周及 12 周的临床吞咽障碍情况（DSRS）和进食途径（表 3；在线补充数据表Ⅱ）。对于功能性评价方法（mRS 和 Barthel 指数），支持 PES 治疗的明显趋势在第 2 周显现出来（但并未在 12 周显现）。其他评价方法在各组之间并无差别（表 3；在线补充数据表Ⅱ）。当评估预先设定的亚组时，在临床吞咽障碍（DSRS）和按年龄及 PAS 值而入组之间呈现出明显的相互作用（见在线补充数据图Ⅰ）。在随机分组之后（和可能与 VFS 相关而不是与后续的 PES 治疗或假治疗相关），出现胸部感染和肺炎的患

表 2 分配入组治疗有效人群的 2 周时的 PAS 值

	全部（*N*=126）	PES 治疗（*N*=70）	假治疗（*N*=56）	*OR*/MD（95%*CI*），校正	*P* 值	*OR*/MD（95%*CI*），未校正	*P* 值
基线							
PAS（/8）	4.8（2.0）	4.8（2.1）	4.7（1.9）	…	…	…	…
2 周时的初级结果							
所有丸剂平均值（/8）	3.6（2.0）	3.7（2.0）	3.6（1.9）	0.14（-0.37~0.64）	0.6	0.06（-0.62~0.74）	0.86
从基线的变化值	-1.2（1.8）	-1.2（1.8）	-1.2（1.8）	0.14（-0.37~0.64）	0.6	0.00（-0.62~0.61）	1
任何一次 PAS>3（%）	105（83.3）	60（85.7）	45（80.4）	1.22（0.29~5.15）	0.79	1.47（0.57~3.75）	0.42
12 周时的结果							
所有丸剂平均值（/8）	3.2（2.1）	3.3（2.2）	3.0（2.1）	0.29（-0.04~0.99）	0.41	0.24（-0.6~1.08）	0.57
任何一次 PAS>3（%）	69（72.6）	36（70.6）	33（75.0）	0.62（0.20~1.90）	0.41	0.80（0.32~1.99）	0.63
重复测定							
平均值（/8）*	…	4.1（2.3）	3.9（2.3）	0.51（-0.23~1.25）	0.18	0.19（-0.67~1.04）	0.67

注：所有患者都接受基线状态和 2 周的诊断性 VFS 检查，并且都接受至少 1 个疗程治疗。表中数据代表数值（%）、中位数（四分位数间距）或均值（标准差）。使用校正和未校正的多元线性回归、有序 logistic 回归或二元 logistic 回归进行分析。*CI*：可信区间；MD：平均差；*OR*：比值比；PAS：渗透误吸评分；PES：咽部电刺激方法。
*包括死亡：PAS=9。

者数量在 2 组之间差异无显著性：PES 治疗组 21 例，假治疗组 11 例（*P*=0.19）。随访结束时严重不良事件的总发生率在 2 组之间差异无显著性，任何一组中均未发生设备相关的不良事件（见在线补充数据表Ⅲ）。在随访期间，所有原因导致的死亡累积风险在 2 组之间差异无显著性（见在线补充数据图Ⅱ）。操作 PES 治疗设备的调查人员认为治疗装备易于使用；但是，1/3 的调查人员认为插入导管有困难（见在线补充数据表Ⅳ）。

从 STEPS 到先前试验的一个总结性的 meta 分析中[9,11]，随机分配到 PES 治疗组和假治疗组的 PAS 值差异无显著性（见在线补充数据图Ⅲ）。相比之下，比起随机分配到假治疗组的患者，接受 PES 治疗患者的 DSRS 远远降低，平均差值为 −0.94（95% 可信区间，−1.85~−0.03；*P*=0.04，见在线补充数据图Ⅳ）。

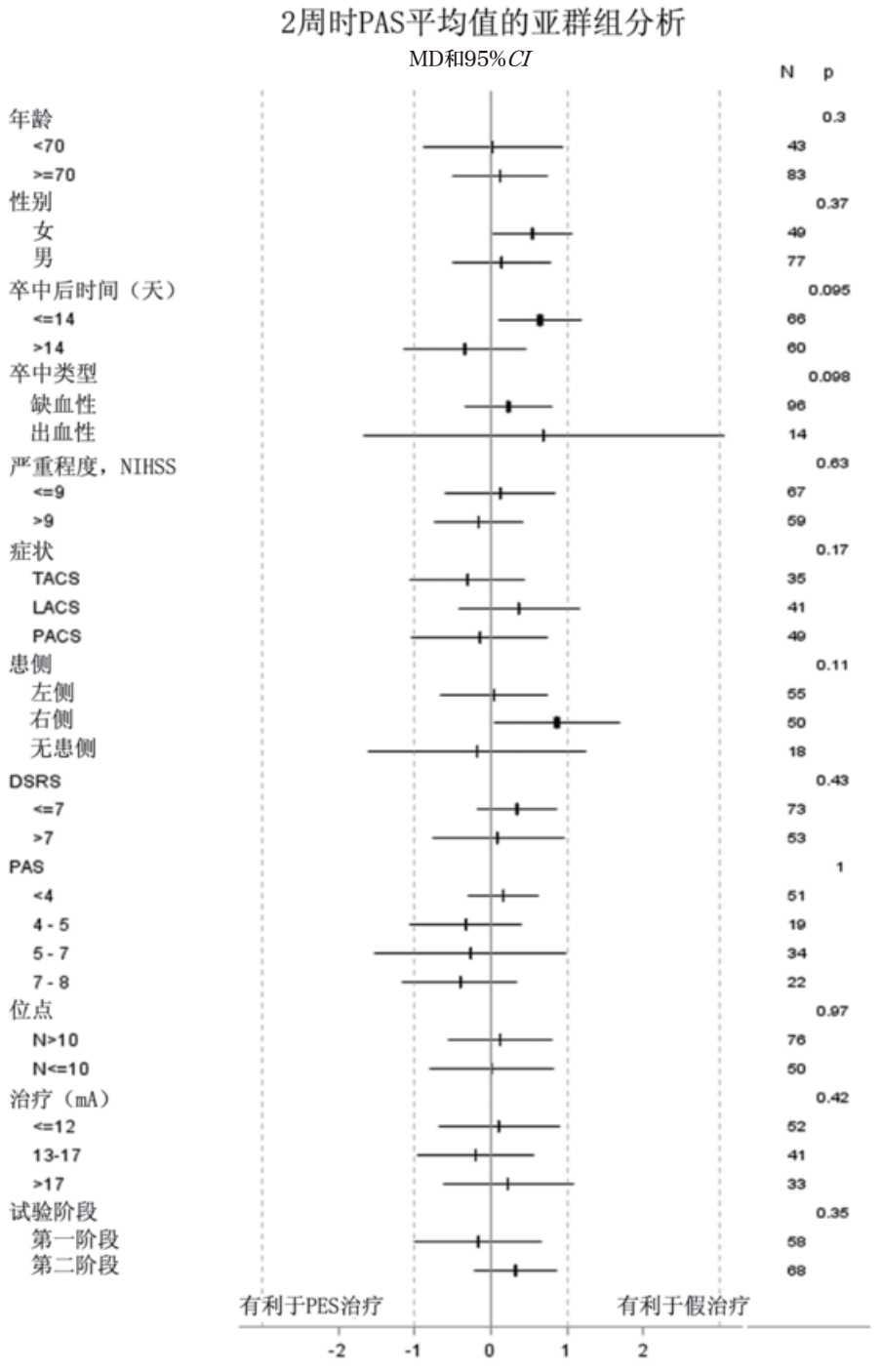

图 2 在预先设定的亚组基线状态下，应用渗透误吸评分表示的治疗效果，采用校正的多次线性回归进行分析。注：MD：平均差；*CI*：可信区间；DSRS：吞咽障碍严重程度评分；LACS：腔隙性循环综合征；NIHSS：美国国立卫生院卒中评分量表；PACS：部分前循环综合征；PAS：渗透误吸评分；PES：咽部电刺激方法；TACS：全部前循环综合征。

讨论

对于卒中后吞咽障碍的患者，应用 PAS 值和吞咽障碍严重程度评分 DSRS 进行评估，PES 治疗对造影剂误吸或临床吞咽障碍并无明显效果。同样，PES 治疗对依赖性（mRS）、功能丧失（Barthel 指数）及损伤程度（NHISS）也没有影响。其中安全性问题没有被证实。

出现如此多的中性结果的原因尚不清楚，但是以下多种可能性有待验证。

第一，PES 治疗可能对卒中后吞咽障碍没有效果，然而这在之前的一个关于卒中后早期 PES 治疗阳性个体的 meta 分析看来是不太可能的，这个 meta 分析是对 DSRS 的阳性总结[9,11,12]，以及多发性硬化和气管切开的卒中患者的阳性试验[21,22]。

第二，在基线处的吞咽障碍严重程度决定治疗成功的可能性。对于急性卒中，想要研究轻度病损患者群体的治疗效果难度较大，这是因为很多患者都自行恢复了正常功能；在这种情况下，轻度吞咽障碍可能会自发缓解。重要的是，德国的主管当局限制招募的患者只能是自主同意进入试验的，这样就导致入组患者都是轻度卒中和误吸，这样一个决定会对很多干预措施的有效性产生影响。尽管 STEPS（PAS=4.8）的平均基础 PAS 值与既往 PES 治疗卒中试验相近（4.3[12]；见在线补充数据表Ⅴ），但是却低于一个关于多发性硬化的阳性试验的数值（PAS=6.5[21]）。有关联的是，在既往研究中随机进入假 PES 治疗组的患者倾向于 PAS 和 DSRS 进展很小或没有总体的进展，但是本研究显示假 PES 治疗患者的 STEPS 显示有进展（见在线补充数据表Ⅴ）。VFS 和吞咽障碍及其严重程度诊断的潜在关联是容易被混淆的；尤其是，PAS 值在对照小团造影剂饮用期间有较大变动。另外，VFS 并不是在很多试验点都方便获取，从而使得招募受到限制。基于前期的初步研究，本研究选择了 PAS 值作为主要观察指标的评价方式，初步

表3 分配入组的患者中至少接受1次治疗或假治疗的患者和可以被测量出结果的患者的临床和安全性结果

	人数	全部	PES治疗	假治疗	*ORIHRIMD*	*P*值校正	*ORIHRIMD*	*P*值校正
2周								
DSRS（/12）*	133	5.1（3.8）	5.2（4.1）	4.9（3.6）	0.31（-0.56~1.18）	0.49	0.23（-1.07~1.54）	0.72
NIHSS（/42）*	134	9.6（7.2）	9.0（7.4）	10.2（7.1）	-0.05（-1.42~1.32）	0.94	-1.19（-3.64~1.26）	0.34
mRS（/6）*	134	3.9（1.1）	3.7（1.2）	4.1（1.0）	0.53（0.23~1.22）	0.14	0.49（0.26~0.92）	0.028
BI（/100）*	134	36.2（34.9）	41.3（37.2）	29.8（31.0）	1.57（-3.60~6.73）	0.55	11.45（-0.22~23.13）	0.055
死亡（%）	141	2（1.4）	1（1.3）	1（1.6）	…	…	0.81（0.05~13.13）	0.88
12周								
DSRS（/12）*	124	4.2（5.1）	4.4（5.2）	3.9（5.1）	1.01（-0.44~2.46）	0.17	0.58（-1.23~2.39）	0.53
EQ-5DasHUS（/1）*	113	0.02（0.40）	0.08（0.41）	-0.04（0.39）	0.13（0.00~0.27）	0.054	0.12（-0.03~0.27）	0.11
EQ-VAS*	105	50.3（30.7）	51.6（30.1）	48.6（31.7）	-4.17（-15.22~6.88）	0.46	3.03（-8.70~14.76）	0.61
处置情况（%）					0.66（0.30~1.49）	0.32	0.63（0.31~1.26）	0.19
家		30（21.3）	20（25.6）	10（15.9）	…	…	…	…
公共机构		93（66.0）	49（62.8）	44（69.8）	…	…	…	…
死亡		18（12.8）	9（11.5）	9（14.3）	…	…	…	…
事件发生事件								
被排除（天）	141	28.2（22.8）	27.7（22.7）	28.7（23.0）	-0.33（-7.79~7.12）	0.93	-0.97（-9.72~7.78）	0.83
死亡（%）	141	18（12.8）	9（11.5）	9（14.3）	1.11（0.34~3.59）	0.86	0.79（0.32~2.00）	0.62

注：BI：Barthel指数；DSRS：吞咽障碍严重程度等级评定；EQ-5D：欧洲生活质量-5维；EQ-VAS：欧洲生活质量可视模拟评分；*HR*：危险系数；HUS：健康利用状态；*MD*：平均差；mRS：改良Rankin量表；NIHSS：美国国立卫生院卒中评分量表；*OR*：比值比；PES：咽部电刺激方法。

*包括死亡：NHISS=43，DSRS=13，mRS=6，BI=-5，HUS=0。

研究显示在PES治疗组[8,9]中这种方法有明显的进展，但是也发现单独PAS值无法获取吞咽效率和像使用高浓度液体饮剂那样单位时间内咽部残留的检测。

第三，关于严重程度和自发缓解的问题，招募时处于卒中早期的患者组成一个复合的组群，组群里是严重吞咽障碍患者和不治疗即可缓解的较轻吞咽障碍患者。然而，较晚招募进入试验的患者中有严重或顽固吞咽障碍的比例增加。在实际情况中，STEPS和既往试验各自招募的都是卒中后2周左右的患者[12]。

第四，参与者或多或少接受了积极的语言治疗，这个环节可能也对附加的PES治疗效果有混杂影响。

第五，PES治疗组患者可能接受的是低水平刺激的治疗，因为在STEPS中平均水平（平均治疗电流为14.8 mA）低于以前卒中阳性试验中所用的水平（16.8 mA[12]）。PES治疗组中有58%的参与者，被给予低于10.2 mA（既往试验中标准差平均值为-1[12]）的治疗电流水平或小于等于0 mA的阈值水平进行治疗，这样的刺激治疗量是不够的。重要的是，已有研究表明，刺激量级与误吸的进展有关[8]。调查人员关心患者的潜在伤害似乎可以解释这个情况，尽管研究没有显示关于有伤害的证据，而且PES在高达50 mA（基础设备站可运载的最高电流）下运行也可能是安全的，这在另一个针对卒中患者的研究[22]中已有显示。

最后，假PES治疗组患者的阈值水平以及耐受水平的评估可能代表刺激的一个要素。例如，一个被分配到假PES治疗组，但是阈值和耐受电流值都比较高的参与者，将会接受可能的治疗量刺激，时长10~20 min（而PES治疗组患者的治疗时长为30 min以上）。这些对于STEPS结果可能的解释为今后PES治疗试验和其他仪器试验的设计和调查人员的培训提供了线索。

STEPS有一些优势，包括与既往PES研究相关的大样本含量；普遍性源于宽的入组标准，纳入了缺血性和出血性卒中，皮层的、腔隙性的、后循环的综合征和宽的时间窗；在欧洲的多个国家招募参与者；治疗分组的中心性设盲；对多种误吸、吞咽障碍、功能性和安全性的预期结果汇总；以及卒中病房中的优质护理服务。

然而，这其中也表现出一些局限性。第一，有195例患者获准进入试验，162例患者被随机分配入组，但是仅有126例患者接受了至少1个疗程治疗并且同时有基础治疗的PAS值。一些因素可以进行解释，包括退出试验和插入导管治疗失败（图1）。一份修订的操作流程指出，治疗导管必须在随机分配入组之前而不是之后进行插入，这样以减少那些被随机分配入组但是不能接受治疗的患者数量。第二，对141例患者实施了PES治疗，但是有15例患者无法在基础状态和2周时实施VFS，因此要从最初的分析中除去这些患者。第三，PES的实施采用的是单盲的方法，患者不知道具体实施情况，但是并未对实施人员进行设盲。某些接受PES治疗的患者可能感觉到刺激，但被分配到假PES治疗组的患者可能感觉到阈值测试时的刺激，而这种刺激在实际治疗时并不存在。然而，第2周、第6周和第12周对临床结果的评定是由训练有素的人员进行评估的，这些人员不知道治疗分配的情况，也不参与所招募患者的住院护理。并且，VFS影像是由同样被设盲、不知道随机分组的放射科医生或语言治疗师来进行判定的。

综上所述，本研究发现PES治疗不能减少放射性吸入或临床吞咽障碍。这个结果与之前一个关于PES治疗卒中后吞咽障碍的小样本试验meta分析不同，之前的试验结果可能有其他混杂因素存在，这些因素包括招募的患者是轻度的吞咽障碍、PES治疗剂量不足和可能给予对照患者治疗量刺激。鉴于这其中的差异以及小样本试验高估治疗效果的潜在风险，关于伴有严重吞咽障碍或要求重症监护（包括辅助通气）的卒中患者的进一步的研究已在计划之中。